Search Page 161

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 NEWS  4  Jul  7  PATOSWO Coverage Extended to 1978 through 1982
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=> s library and (combinatorial or species or organism

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=> s library and (combinatorial or species or organism)

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L1        34117 LIBRARY AND (COMBINATORIAL OR SPECIES OR ORGANISM)

=> s l1 and (genom? or cdna)

L2        23768 L1 AND (GENOM? OR CDNA)

=> s l2 and ((plurality or multiple) (3a) (species or organism))

   2 FILES SEARCHED...
L3          169 L2 AND ((PLURALITY OR MULTIPLE) (3A) (SPECIES OR ORGANISM))

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   2 FILES SEARCHED...
L4          140 L2 AND ((PLURALITY OR MULTIPLE) (3W) (SPECIES OR ORGANISM))

=> s l4 and combinatorial

L5            3 L4 AND COMBINATORIAL

=> d 1-3 bib ab


L5   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 1999 ACS
AN   1998:493199  CAPLUS
DN   129:118769
TI   Identification of genes involved in metabolic pathways and the use of
     combinatorial DNA libraries to generate novel molecular
     diversity
IN   Peterson, Todd C.; Foster, Lyndon M.; Brian, Paul
PA   Chromaxome Corporation, USA
SO   U.S., 80 pp. Cont.-in-part of U.S. Ser. No. 639,255.
     CODEN: USXXAM
DT   Patent
LA   English
FAN.CNT 4
     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
     ---------------    ----  --------       ---------------   --------
PI   US 5783431          A    19980721       US 96-738944      19961024
     US 5824485          A    19981020       US 96-639255      19960424
     WO 9817811          A1   19980430       WO 97-US19958     19971024
         W:  AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH,
             HU, ID, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG,
             MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
             GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
             GN, ML, MR, NE, SN, TD, TG
     AU 9851632          A1   19980515       AU 98-51632       19971024
PRAI US 96-639255      19960424
     US 95-427244      19950424
     US 95-427348      19950424
     US 96-738944      19961024
     WO 97-US19958     19971024
AB   A novel drug discovery system for generating and screening mol. diversity
     using combinatorial expression libraries of genes from
     organism manufg. compds. of potential therapeutic use is
```

described. The system provides methods for mixing and cloning genetic materials from a **plurality** of **species** of **organisms** in **combinatorial** gene expression **libraries** to generate novel metabolic pathways and classes of compds. The method is applicable to **organisms** that cannot be easily cultured. The system also provides mobilizable **combinatorial** gene expression **libraries** that can be transferred from one **species** of host **organism** to another for expression. Also provided are specialized cloning vectors for making mobilizable gene expression **libraries**. The system also involves methods for pre-screening or identifying for host **organisms** contg. a **library** that are capable of generating such novel pathways and compds. The method is demonstrated by making **libraries** from Gram-neg. marine bacteria in expression vectors for Streptomyces. Colonies identified as hybridizing with probes for genes of polyketide biosynthesis were picked, tested for ability to inhibit bacterial growth and further tested in random combinations. The test identified a no. of combinations that gave rise to antibacteria effects.

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 1999 ACS
AN 1998:268629 CAPLUS
DN 128:318004
TI Identification of genes involved in metabolic pathways and the use of **combinatorial** DNA **libraries** to generate novel molecular diversity
IN Peterson, Todd C.; Foster, Lyndon M.; Brian, Paul
PA Chromaxome Corp., USA
SO PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9817811	A1	19980430	WO 97-US19958	19971024
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, ID, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5783431	A	19980721	US 96-738944	19961024
	AU 9851632	A1	19980515	AU 98-51632	19971024
PRAI	US 96-738944	19961024			
	US 96-639255	19960424			
	WO 97-US19958	19971024			

AB A novel drug discovery system for generating and screening mol. diversity using **combinatorial** expression **libraries** of genes from **organism** manufg. compds. of potential therapeutic use is described. The system provides methods for mixing and cloning genetic materials from a **plurality** of **species** of **organisms** in **combinatorial** gene expression **libraries** to generate novel metabolic pathways and classes of compds. The method is applicable to **organisms** that cannot be easily cultured. The system also provides mobilizable **combinatorial** gene expression **libraries** that can be transferred from one **species** of host **organism** to

another for expression. Also provided are specialized cloning vectors for making mobilizable gene expression **libraries**. The system also involves methods for pre-screening or identifying for host **organisms** contg. a **library** that are capable of generating such novel pathways and compds. The method is demonstrated by making **libraries** from Gram-neg. marine bacteria in expression vectors for Streptomyces. Colonies identified as hybridizing with probes for genes of polyketide biosynthesis were picked, tested for ability to inhibit bacterial growth and further tested in random combinations. The test identified a no. of combinations that gave rise to antibacteria effects.

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 1999 ACS
AN 1996:761917 CAPLUS
DN 126:27672
TI Methods for generating and screening novel metabolic pathways using mixed **combinatorial** expression **libraries** from several **species**
IN Thompson, Katie A.; Foster, Lyndon M.; Peterson, Todd C.
PA Chromaxome Corp., USA
SO PCT Int. Appl., 144 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9634112	A1	19961031	WO 96-US6003	19960424
	W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY, KG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2219136	AA	19961031	CA 96-2219136	19960424
	AU 9658049	A1	19961118	AU 96-58049	19960424
	EP 822990	A1	19980211	EP 96-913270	19960424
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1189191	A	19980729	CN 96-194988	19960424
	JP 11504218	T2	19990420	JP 96-532786	19960424
PRAI	US 95-427244	19950424			
	US 95-427348	19950424			
	WO 96-US6003	19960424			

AB A novel drug discovery system for generating novel metabolites and for screening these metabolites for therapeutic use is described. The system uses **combinatorial** expression **libraries** that contain DNA from several **species** to generate novel metabolic pathways and classes of compds. Methods for pre-screening or identifying host **organisms** contg. a **library** that are capable of generating such novel pathways and compds. using are also described. The host **organisms** may be useful in drug screening for particular diseases, and in com. prodn. of compds. of interest. The methods of the invention are also useful in preserving the **genomes** of **organisms** that are known or prospective sources of drugs.

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FILE 'MEDLINE, BIOSIS, CAPLUS' ENTERED AT 18:52:33 ON 12 JUL 1999
L1 34117 S LIBRARY AND (COMBINATORIAL OR SPECIES OR ORGANISM)
L2 23768 S L1 AND (GENOM? OR CDNA)
L3 169 S L2 AND ((PLURALITY OR MULTIPLE) (3A) (SPECIES OR ORGANISM))
L4 140 S L2 AND ((PLURALITY OR MULTIPLE) (3W) (SPECIES OR ORGANISM))
L5 3 S L4 AND COMBINATORIAL

=> d l4 1-10 bib ab

L4 ANSWER 1 OF 140 MEDLINE
AN 1999216440 MEDLINE
DN 99216440
TI Cloning and chromosomal mapping of a gene isolated from thymic stromal cells encoding a new mouse type II membrane serine protease, epithin, containing four LDL receptor modules and two CUB domains.
AU Kim M G; Chen C; Lyu M S; Cho E G; Park D; Kozak C; Schwartz R H
CS Laboratory of Cellular and Molecular Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-0420, USA.
SO IMMUNOGENETICS, (1999 May) 49 (5) 420-8.
Journal code: GI4. ISSN: 0093-7711.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-AF042822
EM 199908
EW 19990801
AB We cloned and sequenced a mouse gene encoding a new type of membrane bound serine protease (epithin) containing a multidomain structure. The initial **cDNA** clone was found previously in a polymerase chain reaction (PCR)-based subtractive **library** generated from fetal thymic stromal cells, and the message was shown to be highly expressed in a thymic epithelial nurse cell line. A clone isolated from a severe combined immunodeficiency (SCID) thymus **library** and extended to its full length at the 5' end with the RACE technique contains an open reading frame of 902 amino acids. Based on the sequence of this clone, the predicted protein structure is a type II membrane protein with a C-terminal serine protease domain linked to the membrane by four low density lipoprotein receptor modules and two CUB domains. High message expression by northern blotting was detected in intestine, kidney, lung, SCID, and Rag-2(-/-) thymus, and 2-deoxyguanosine-treated fetal thymic rudiment, but not in skeletal muscle, liver, heart, testis, and brain. Sorted MHC class II+ and II- fetal thymic stromal cells were positive for expression by reverse transcriptase-PCR, whereas CD45(+) thymocytes were not. The gene was found in chicken and **multiple** mammalian **species** under low stringency Southern hybridization conditions. Under high stringency conditions, only a single gene per haploid **genome** was identified in the mouse. This gene, Prss14 (protease, serine, 14), was mapped to mouse chromosome 9 and is closely linked to the Fli1 (Friend leukemia integration 1) gene.

L4 ANSWER 2 OF 140 MEDLINE

AN 1999062010 MEDLINE
DN 99062010
TI The univector plasmid-fusion system, a method for rapid construction of recombinant DNA without restriction enzymes.
AU Liu Q; Li M Z; Leibham D; Cortez D; Elledge S J
CS Howard Hughes Medical Institute Verna and Marrs McLean Department of Biochemistry Baylor College of Medicine One Baylor Plaza Houston Texas 77030 USA.
NC GM44664 (NIGMS)
SO CURRENT BIOLOGY, (1998 Dec 3) 8 (24) 1300-9.
Journal code: B44. ISSN: 0960-9822.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
EW 19990402
AB Background:. Modern biological research is highly dependent upon recombinant DNA technology. Conventional cloning methods are time-consuming and lack uniformity. Thus, biological research is in great need of new techniques to rapidly, systematically and uniformly manipulate the large sets of genes currently available from **genome** projects. Results:. We describe a series of new cloning methods that facilitate the rapid and systematic construction of recombinant DNA molecules. The central cloning method is named the univector plasmid-fusion system (UPS). The UPS uses Cre-lox site-specific recombination to catalyze plasmid fusion between the univector - a plasmid containing the gene of interest - and host vectors containing regulatory information. Fusion events are genetically selected and place the gene under the control of new regulatory elements. A second UPS-related method allows for the precise transfer of coding sequences only from the univector into a host vector. The UPS eliminates the need for restriction enzymes, DNA ligases and many in vitro manipulations required for subcloning, and allows for the rapid construction of multiple constructs for expression in **multiple organisms**. We demonstrate that UPS can also be used to transfer whole **libraries** into new vectors. Additional adaptations are described, including directional PCR cloning and the generation of 3' end gene fusions using homologous recombination in Escherichia coli. Conclusions:. Together, these recombination-based cloning methods constitute a new comprehensive approach for the rapid and efficient generation of recombinant DNA that can be used for parallel processing of large gene sets, a feature that will facilitate future **genomic** analysis.

L4 ANSWER 3 OF 140 MEDLINE
AN 1998236152 MEDLINE
DN 98236152
TI Cloning and characterization of the guinea pig C5a anaphylatoxin receptor: interspecies diversity among the C5a receptors.
AU Fukuoka Y; Ember J A; Yasui A; Hugli T E
CS Department of Immunology, The Scripps Research Institute, La Jolla, CA 92037, USA.
NC R01-DE10992 (NIDR)
SO INTERNATIONAL IMMUNOLOGY, (1998 Mar) 10 (3) 275-83.
Journal code: AY5. ISSN: 0953-8178.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 199808
EW 19980802
AB The anaphylatoxin C5a receptor (C5aR, CD88 in man) plays a prominent role in mediating inflammatory and host defense processes. Direct evidence of C5aR involvement in host defense mechanisms was demonstrated recently using C5aR knockout mice. Mice deficient in C5aR were unable to clear intrapulmonary-instilled bacteria. The guinea pig system is perhaps unique for exhibiting cross-reactivity with human complement components and its high sensitivity to anaphylatoxins. Therefore, we cloned the guinea pig C5aR from a megakaryocyte **cDNA library**. The deduced amino acid sequence of guinea pig C5aR is 67% identical to human, 61.6% to dog, 60.2% to mouse and 63.6% to rat C5aR. Transient expression of guinea pig C5aR in COS-7 cells and stable expression on L cell fibroblasts were confirmed by FACS analysis. Competitive binding studies using [125I]C5a and stimulation of calcium mobilization by C5a proved that functional C5aR was expressed on these stably transfected L cells. The N-terminal extracellular region of guinea pig C5aR was five to seven residues shorter than the same region in C5aR from other **species** and sequence homology was limited to 11%. Other outer membrane loops were also poorly conserved (8-33%) when compared across five **species**. Transmembrane segments were highly conserved between these various **species** (46-86%). Guinea pig C5aR binds human C5a, therefore residues critical for C5a binding have been conserved between these **species**. Sequence comparison of C5aR from **multiple species** permits conserved elements of the ligand binding sites to be elucidated.

L4 ANSWER 4 OF 140 MEDLINE
AN 1998215351 MEDLINE
DN 98215351
TI Mesenchymal stem cell surface antigen SB-10 corresponds to activated leukocyte cell adhesion molecule and is involved in osteogenic differentiation.
AU Bruder S P; Ricalton N S; Boynton R E; Connolly T J; Jaiswal N; Zaia J; Barry F P
CS Osiris Therapeutics, Inc., Baltimore, Maryland 21231-2001, USA.. SBruder@Osiristx.com
SO JOURNAL OF BONE AND MINERAL RESEARCH, (1998 Apr) 13 (4) 655-63. Journal code: 130. ISSN: 0884-0431.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
AB Bone marrow contains a rare population of mesenchymal stem cells (MSCs) capable of giving rise to multiple mesodermal tissues including bone, cartilage, tendon, muscle, and fat. The cell surface antigen recognized by monoclonal antibody SB-10 is expressed on human MSCs but is lost during their developmental progression into differentiated phenotypes. Here we report on the immunopurification of the SB-10 antigen and its identification as activated leukocyte-cell adhesion molecule (ALCAM). Mass spectrometry establishes that the molecular mass of ALCAM is 80,303 +/-

193 Da and that it possesses 17,763 +/- 237 Da of N-linked oligosaccharide substituents. Molecular cloning of a full-length **cDNA** from a MSC expression **library** demonstrates nucleotide sequence identity with ALCAM. We also identified ALCAM homologs in rat, rabbit, and canine MSCs, each of which is over 90% identical to human ALCAM in their peptide sequence. The addition of antibody SB-10 Fab fragments to human MSCs undergoing osteogenic differentiation in vitro accelerated the process, thereby implicating a role for ALCAM during bone morphogenesis and adding ALCAM to the group of cell adhesion molecules involved in osteogenesis. Together, these results provide evidence that ALCAM plays a critical role in the differentiation of mesenchymal tissues in **multiple species** across the phylogenetic tree.

L4 ANSWER 5 OF 140 MEDLINE
AN 97225904 MEDLINE
DN 97225904
TI Human choline acetyltransferase mRNAs with different 5'-region produce a 69-kDa major translation product.
AU Misawa H; Matsuura J; Oda Y; Takahashi R; Deguchi T
CS Department of Neurology, Tokyo Metropolitan Institute for Neuroscience, Fuchu City, Japan.. hmisawa@tmin.ac.jp
SO BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1997 Mar) 44 (2) 323-33. Journal code: MBR. ISSN: 0169-328X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-D82339; GENBANK-D82340; GENBANK-D82341; GENBANK-D82342
EM 199709
AB Choline acetyltransferase (ChAT, EC 2.3.1.6) is the biosynthetic enzyme for acetylcholine. We have previously shown that **multiple** ChAT mRNA **species** with different 5'-noncoding regions are expressed in the rat and mouse. However, the diversity of ChAT mRNA **species** in human has not completely been elucidated. In this work N1- and N2-type ChAT **cDNAs** were cloned from a human brain **cDNA library** and the N-exon located in the human ChAT gene. Polymerase chain reaction analysis indicates that four **species** of ChAT mRNAs (R-, N1-, N2- and M-types) are produced in human brain and spinal cord. In all human transcripts, the ATG initiation codon in the rat, mouse and pig was replaced by ACG, which does not serve as an initiation codon for translation. In vitro translation and mammalian expression analyses revealed that N1-, N2- and R-type mRNAs give rise to a single 69 kDa enzyme, while M-type mRNA produces both 82 and 69 kDa enzymes. The translation efficiency of M-type mRNA was lower than that of the other mRNA **species**. Moreover, the translation efficiency of human ChAT mRNAs was considerably lower than that of rat ChAT mRNA, suggesting that the ATG codons for human ChAT are unfavorable for translation initiation compared with the initiation codon for rat ChAT. These results provide rational explanations for the previous reports that human ChAT protein purified from the brain and placenta had 66-70 kDa molecular mass, and that ChAT activity in a single motor neuron of human was far lower than that of other vertebrates. Sequencing of monkey ChAT gene showed that the initiation ATG in rodent ChAT was also replaced by ACA in the monkey.

L4 ANSWER 6 OF 140 MEDLINE
AN 97099215 MEDLINE
DN 97099215
TI Steroid sulfotransferases.

AU Luu-The V; Bernier F; Dufort I
CS Medical Research Council Group in Molecular Endocrinology, CHUL Research Center, Quebec, Canada.
SO JOURNAL OF ENDOCRINOLOGY, (1996 Sep) 150 Suppl S87-97.
Journal code: I1J. ISSN: 0022-0795.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
AB Human dehydroepiandrosterone sulfotransferase (DHEA-ST) catalyzes the sulfonation of DHEA, cholesterol, pregnenolone as well as androsterone. RNA blot analysis shows two DHEA-ST mRNA **species** of 1.3 and 1.8 kb that are expressed similarly in liver and adrenals. To determine whether the form expressed in adrenals is distinct or identical with the one expressed in liver, we have cloned and sequenced the 1.8 kb DHEA-ST **cDNA** from human adrenal **cDNA library**. Except for one nucleotide difference, the human adrenal and liver DHEA-ST **cDNAs** are identical. Using expression vectors containing the chloramphenicol acetyltransferase (CAT) reporter gene ligated to various fragments of the DHEA-ST gene promoter, we have shown that DHEA-ST gene promoter activity is stimulated by estradiol (E2). The E2 stimulation is inhibited by the anti-estrogen EM-139. In contrast to human DHEA-ST, guinea pig hydroxysteroid sulfotransferases show high substrate- and stereo-selectivity. We have cloned a chiral-specific pregnenolone sulfotransferase (PREG-ST) which catalyzes mainly the transformation of pregnenolone to pregnenolone sulfate. Estrogen sulfotransferase catalyzes the conversion of estrone and estradiol to their inactive sulfated forms and could thus play a major role in the control of estrogen levels in target tissues. Recently, using a probe derived from bovine estrogen sulfotransferase, we have cloned a **cDNA** and gene that we first named human estrogen sulfotransferase (hEST) since the expressed enzyme is able to transform estrone to estrone sulfate. Actually, the Hugo nomenclature committee named this gene STM gene because it also codes for monoamine-sulfating phenol-sulfotransferase (M-PST). hEST1 possesses the same coding and 3'-untranslated region as human brain aryl sulfotransferase (HAST) and M-PST, but different 5'-noncoding region. Analysis of hEST1 gene sequence indicates that hEST1 and HAST3 or M-PST mRNA **species** are transcribed from a single hEST1 gene by alternative promoters using two separate exon 1, named exon Ia and exon Ib. We also described the identification of a third mRNA **species** (M-PST gamma) issued from the STM gene and the characterization of the structure of the phenol-sulfating phenolsulfotransferase (STP) gene that is highly homologous to the STM gene. Similar to STM, the STP gene generates **multiple** mRNA **species** that differ only in the 5'-untranslated sequence.

L4 ANSWER 7 OF 140 MEDLINE
AN 97094876 MEDLINE
DN 97094876
TI The deletion of 14 amino acids in the seventh transmembrane domain of a naturally occurring calcitonin receptor isoform alters ligand binding and selectively abolishes coupling to phospholipase C.
AU Shyu J F; Inoue D; Baron R; Horne W C
CS Department of Cell Biology , Yale University School of Medicine, New Haven, Connecticut 06520-8044, USA.
NC DE-04724 (NIDR)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 6) 271 (49) 31127-34.
Journal code: HIV. ISSN: 0021-9258.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-U66365
EM 199703
EW 19970302
AB The **cDNA** that encodes the rabbit calcitonin receptor was cloned by screening a rabbit osteoclast **library**. Reverse transcription-polymerase chain reaction amplification of calcitonin receptor sequences from rabbit osteoclast RNA yielded **cDNAs** that encode two isoforms of the calcitonin receptor. One isoform is homologous to the C1a isoform previously identified in **multiple** cell types and **species**, while the second, designated CTRDeltae13, is a previously unidentified isoform that is apparently generated by alternative splicing during mRNA processing that deletes exon 13, resulting in the absence of 14 amino acids in the predicted seventh transmembrane domain. Expression of mRNA transcripts encoding the two isoforms varies in a tissue-specific manner, with CTRDeltae13 accounting for less than 15% of the total calcitonin receptor mRNA in osteoclasts, kidney, and brain, but comprising at least 50% of the transcripts in skeletal muscle and lung. The two isoforms were expressed, and the ligand binding and signal transduction properties were characterized. Deletion of the residues in the seventh transmembrane domain in CTRDeltae13 reduced the binding affinity for salmon and human calcitonin by more than 10-fold and approximately 2-fold, respectively, resulting in a receptor that failed to discriminate between the two forms of calcitonin. Both isoforms activated adenylyl cyclase, with EC50 values consistent with the difference in ligand affinities. In contrast, only the C1a isoform, but not the CTRDeltae13 isoform, activated phospholipase C. Thus, while the CTRDeltae13 remains active despite the deletion of a significant portion of its seventh transmembrane domain, it has significantly altered ligand recognition and signal transduction properties.

L4 ANSWER 8 OF 140 MEDLINE
AN 96254561 MEDLINE
DN 96254561
TI Characterization of IS1272, an insertion sequence-like element from Staphylococcus haemolyticus.
AU Archer G L; Thanassi J A; Niemeyer D M; Pucci M J
CS Department of Microbiology/Immunology, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0049, USA.. GARCHER@GEMS.VCU.EDU
NC AI35705 (NIAID)
SO ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1996 Apr) 40 (4) 924-9. Journal code: 6HK. ISSN: 0066-4804.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U35635
EM 199612
AB We have previously shown (G. L. Archer, D. M. Niemeyer, J. A. Thanassi, and M. J. Pucci, Antimicrob. Agents Chemother. 38:447-454, 1994) that some methicillin-resistant staphylococcal isolates contain a partial deletion of the genes (mecR1 and mecI) that regulate the transcription of the methicillin resistance structural gene (mecA). When a fragment of DNA inserted at the point of the mecR1 deletion was used as a probe,

hybridization with multiple bands was detected for Staphylococcus haemolyticus **genomic** DNA. In the present study, DNA sequencing of four unique clones recovered from a lambda **library** of S. haemolyticus revealed identical 1,934-bp elements. Each element, designated IS1272, contained 16-bp terminal inverted repeats (sequence identity, 15 of 16 bp) and two open reading frames of 819 and 687 bp; there were no flanking target site duplications. Database searches yielded amino acid homology with proteins predicted to be encoded by open reading frames from a putative insertion sequence element from Enterococcus hirae. DNA probes from each end and the middle of IS1272 were hybridized with restriction endonuclease-digested **genomic** DNA from clinical S. haemolyticus, Staphylococcus epidermidis, and Staphylococcus aureus isolates. Each of the 20 or more copies of the element found in S. haemolyticus isolates was intact, and copies were found in most chromosomal SmaI fragments. S. aureus and S. epidermidis isolates contained mostly incomplete fragments of the element, and there were many more hybridizing fragments in methicillin-resistant than in methicillin-susceptible isolates. IS1272, which appears to be primarily resident in S. haemolyticus, has disseminated to **multiple** staphylococcal **species** and is prevalent in multiresistant isolates.

L4 ANSWER 9 OF 140 MEDLINE
AN 96042128 MEDLINE
DN 96042128
TI Human Mig chemokine: biochemical and functional characterization.
AU Liao F; Rabin R L; Yannelli J R; Koniaris L G; Vanguri P; Farber J M
CS Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.
NC CA-48059 (NCI)
CA-52001 (NCI)
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1995 Nov 1) 182 (5) 1301-14.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199602
AB Mig is a chemokine of the CXC subfamily that was discovered by differential screening of a **cDNA library** prepared from lymphokine-activated macrophages. The mig gene is inducible in macrophages and in other cells in response to interferon (IFN)-gamma. We have transfected Chinese hamster ovary (CHO) cells with **cDNA** encoding human Mig and we have derived CHO cell lines from which we have purified recombinant human Mig (rHuMig). rHuMig induced the transient elevation of [Ca2+]i in human tumor-infiltrating T lymphocytes (TIL) and in cultured, activated human peripheral blood-derived lymphocytes. No responses were seen in human neutrophils, monocytes, or Epstein-Barr virus-transformed B lymphoblastoid cell lines. rHuMig was chemotactic for TIL by a modified Boyden chamber assay but rHuMig was not chemotactic for neutrophils or monocytes. The CHO cell lines, IFN-gamma-treated human peripheral-blood monocytes, and IFN-gamma-treated cells of the human monocytic cell line THP-1 all secreted **multiple** and identical HuMig **species** as revealed by SDS-PAGE. Using the CHO-derived rHuMig, we have shown that the **species'** heterogeneity is due to proteolytic cleavage at basic carboxy-terminal residues, and that the proteolysis occurs before

and not after rHuMig secretion by the CHO cells. The major **species** of secreted rHuMig ranged from 78 to 103 amino acids in length, the latter corresponding to the full-length secreted protein predicted from the HuMig **cDNA**. Carboxy-terminal-truncated forms of rHuMig were of lower specific activity compared to full-length rHuMig in the calcium flux assay, and the truncated **species** did not block the activity of the full-length **species**. It is likely that HuMig plays a role in T cell trafficking and perhaps in other aspects of the physiology of activated T cells.

L4 ANSWER 10 OF 140 MEDLINE
AN 95247712 MEDLINE
DN 95247712
TI Characterization of mouse and human GTP cyclohydrolase I genes. Mutations in patients with GTP cyclohydrolase I deficiency.
AU Ichinose H; Ohye T; Matsuda Y; Hori T; Blau N; Burlina A; Rouse B; Matalon R; Fujita K; Nagatsu T
CS Institute for Comprehensive Medical Science, Fujita Health University, Aichi, Japan..
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Apr 28) 270 (17) 10062-71. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
OS GENBANK-D38601; GENBANK-D38602; GENBANK-D38603; GENBANK-U19256; GENBANK-U19257; GENBANK-U19258; GENBANK-U19259
EM 199508
AB GTP cyclohydrolase I is the first and rate-limiting enzyme for the biosynthesis of tetrahydrobiopterin in mammals. Previously, we reported three **species** of human GTP cyclohydrolase I **cDNA** in a human liver **cDNA library** (Togari, A., Ichinose, H., Matsumoto, S., Fujita, K., and Nagatsu, T. (1992) Biochem. Biophys. Res. Commun. 187, 359-365). Furthermore, very recently, we found that the GTP cyclohydrolase I gene is causative for hereditary progressive dystonia with marked diurnal fluctuation, also known as DOPA-responsive dystonia (Ichinose, H., Ohye, T., Takahashi, E., Seki, N., Hori, T., Segawa, M., Nomura, Y., Endo, K., Tanaka, H., Tsuji, S., Fujita, K., and Nagatsu, T. (1994) Nature Genetics 8, 236-242). To clarify the mechanisms that regulate transcription of the GTP cyclohydrolase I gene and to generate **multiple species** of mRNA, we isolated **genomic** DNA clones for the human and mouse GTP cyclohydrolase I genes. Structural analysis of the isolated clones revealed that the GTP cyclohydrolase I gene is encoded by a single copy gene and is composed of six exons spanning approximately 30 kilobases. We sequenced all exon/intron boundaries of the human and mouse genes. Structural analysis also demonstrated that the heterogeneity of GTP cyclohydrolase I mRNA is caused by an alternative usage of the splicing acceptor site at the sixth exon. The transcription start site of the mouse GTP cyclohydrolase I gene and the 5'-flanking sequences of the mouse and human genes were determined. We performed regional mapping of the mouse gene by fluorescence in situ hybridization, and the mouse GTP cyclohydrolase I gene was assigned to region C2-3 of mouse chromosome 14. We identified missense mutations in patients with GTP cyclohydrolase I deficiency and expressed mutated enzymes in Escherichia coli to confirm alterations in the enzyme activity.

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L1        34117 S LIBRARY AND (COMBINATORIAL OR SPECIES OR ORGANISM)
L2        23768 S L1 AND (GENOM? OR CDNA)
L3          169 S L2 AND ((PLURALITY OR MULTIPLE) (3A) (SPECIES OR ORGANISM))
L4          140 S L2 AND ((PLURALITY OR MULTIPLE) (3W) (SPECIES OR ORGANISM))
L5            3 S L4 AND COMBINATORIAL

=> s l2 and ((plurality or multiple) (2w) (species or organism))

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L8   ANSWER 1 OF 57  CAPLUS  COPYRIGHT 1999 ACS
AN   1996:761917  CAPLUS
DN   126:27672
TI   Methods for generating and screening novel metabolic pathways using mixed
     combinatorial expression libraries from several
     species
IN   Thompson, Katie A.; Foster, Lyndon M.; Peterson, Todd C.
PA   Chromaxome Corp., USA
SO   PCT Int. Appl., 144 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 4
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 9634112          A1   19961031      WO 96-US6003     19960424
         W:  AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS,
             JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO,
             NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ,
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BY, KG
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA	2219136	AA	19961031	CA 96-2219136	19960424
AU	9658049	A1	19961118	AU 96-58049	19960424
EP	822990	A1	19980211	EP 96-913270	19960424
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN	1189191	A	19980729	CN 96-194988	19960424
JP	11504218	T2	19990420	JP 96-532786	19960424

PRAI US 95-427244 19950424
US 95-427348 19950424
WO 96-US6003 19960424

AB A novel drug discovery system for generating novel metabolites and for screening these metabolites for therapeutic use is described. The system uses **combinatorial** expression **libraries** that contain DNA from several **species** to generate novel metabolic pathways and classes of compds. Methods for pre-screening or identifying host **organisms** contg. a **library** that are capable of generating such novel pathways and compds. using are also described. The host **organisms** may be useful in drug screening for particular diseases, and in com. prodn. of compds. of interest. The methods of the invention are also useful in preserving the **genomes** of **organisms** that are known or prospective sources of drugs.

L8 ANSWER 2 OF 57 CAPLUS COPYRIGHT 1999 ACS
AN 1996:674690 CAPLUS
DN 126:44309
TI Steroid sulfotransferases
AU Luu-The, V.; Bernier, F.; Dufort, I.
CS CHUL Res. Cent., Laval Univ., Quebec, PQ, G1V 4G2, Can.
SO J. Endocrinol. (1996), 150(Suppl., Proceedings of the International Symposium on DHEA Transformation in Target Tissues, 1995), S87-S97
CODEN: JOENAK; ISSN: 0022-0795
PB Journal of Endocrinology
DT Journal
LA English
AB Human dehydroepiandrosterone sulfotransferase (DHEA-ST) catalyzes the sulfonation of DHEA, cholesterol, pregnenolone as well as androsterone. RNA blot anal. shows two DHEA-ST mRNA **species** of 1.3 and 1.8 kb that are expressed similarly in liver and adrenals. To det. whether the form expressed in adrenals is distinct or identical with the one expressed in liver, we have cloned and sequenced the 1.8 kb DHEA-ST **cDNA** from human adrenal **cDNA library**. Except for one nucleotide difference, the human adrenal and liver DHEA-ST **cDNAs** are identical. Using expression vectors contg. the chloramphenicol acetyltransferase (CAT) reporter gene ligated to various fragments of the DHEA-ST gene promoter, we have shown that DHEA-ST gene promoter activity is stimulated by estradiol (E2). The E2 stimulation is inhibited by the anti-estrogen EM-139. In contrast to human DHEA-ST, guinea pig hydroxysteroid sulfotransferases show high substrate- and stereo-selectivity. We have cloned a chiral-specific pregnenolone sulfotransferase (PREG-ST) which catalyzes mainly the transformation of pregnenolone to pregnenolone sulfate. Estrogen sulfotransferase catalyzes the conversion of estrone and estradiol to their inactive sulfated forms and could thus play a major role in the control of estrogen levels in target tissues. Recently, using a probe derived from bovine estrogen

sulfotransferase, we have cloned a **cDNA** and gene that we first named human estrogen sulfotransferase (hEST) since the expressed enzyme is able to transform estrone to estrone sulfate. Actually, the Hugo nomenclature committee named this gene STM gene because it also codes for monoamine-sulfating phenol-sulfotransferase (M-PST). HEST1 possesses the same coding and 3'-untranslated region as human brain aryl sulfotransferase (HAST) and M-PST, but different 5'-noncoding region. Anal. of hEST1 gene sequence indicates that hEST1 and HAST3 or M-PST mRNA **species** are transcribed from a single hEST1 gene by alternative promoters using two sep. exon I, named exon Ia and exon Ib. We also described the identification of a third mRNA **species** (M-PST.gamma.) issued from the STM gene and the characterization of the structure of the phenol-sulfating phenolsulfotransferase (STP) gene that is highly homologous to the STM gene. Similar to STM, the STP gene generates **multiple** mRNA **species** that differ only in the 5'-untranslated sequence.

L8 ANSWER 3 OF 57 MEDLINE DUPLICATE 1
AN 96254561 MEDLINE
DN 96254561
TI Characterization of IS1272, an insertion sequence-like element from Staphylococcus haemolyticus.
AU Archer G L; Thanassi J A; Niemeyer D M; Pucci M J
CS Department of Microbiology/Immunology, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0049, USA.. GARCHER@GEMS.VCU.EDU
NC AI35705 (NIAID)
SO ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1996 Apr) 40 (4) 924-9. Journal code: 6HK. ISSN: 0066-4804.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U35635
EM 199612
AB We have previously shown (G. L. Archer, D. M. Niemeyer, J. A. Thanassi, and M. J. Pucci, Antimicrob. Agents Chemother. 38:447-454, 1994) that some methicillin-resistant staphylococcal isolates contain a partial deletion of the genes (mecR1 and mecI) that regulate the transcription of the methicillin resistance structural gene (mecA). When a fragment of DNA inserted at the point of the mecR1 deletion was used as a probe, hybridization with multiple bands was detected for Staphylococcus haemolyticus **genomic** DNA. In the present study, DNA sequencing of four unique clones recovered from a lambda **library** of S. haemolyticus revealed identical 1,934-bp elements. Each element, designated IS1272, contained 16-bp terminal inverted repeats (sequence identity, 15 of 16 bp) and two open reading frames of 819 and 687 bp; there were no flanking target site duplications. Database searches yielded amino acid homology with proteins predicted to be encoded by open reading frames from a putative insertion sequence element from Enterococcus hirae.
DNA probes from each end and the middle of IS1272 were hybridized with restriction endonuclease-digested **genomic** DNA from clinical S. haemolyticus, Staphylococcus epidermidis, and Staphylococcus aureus isolates. Each of the 20 or more copies of the element found in S. haemolyticus isolates was intact, and copies were found in most chromosomal SmaI fragments. S. aureus and S. epidermidis isolates

contained mostly incomplete fragments of the element, and there were many more hybridizing fragments in methicillin-resistant than in methicillin-susceptible isolates. IS1272, which appears to be primarily resident in S. haemolyticus, has disseminated to **multiple** staphylococcal **species** and is prevalent in multiresistant isolates.

L8 ANSWER 4 OF 57 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 2
AN 1996:461793 BIOSIS
DN PREV199699184149
TI Isolation and characterization of novel salmon microsatellite loci: Cross-**species** amplification and population genetic applications.
AU Scribner, Kim T. (1); Gust, Judy R.; Fields, Raymond L.
CS (1) Alaska Sci. Cent., Natl. Biol. Serv., 1011 E Tudor Rd., Anchorage, AK 99503 USA
SO Canadian Journal of Fisheries and Aquatic Sciences, (1996) Vol. 53, No. 4, pp. 833-841.
ISSN: 0706-652X.
DT Article
LA English
SL English; French
AB Twenty-two variable number of tandem repeat microsatellite dinucleotide repeat ((GA)-n and (CA)-n) loci were cloned from sockeye salmon (Oncorhynchus nerka) partial **genomic libraries**. Characteristics and optimal polymerase chain reaction (PCR) conditions were defined for each locus. The degree of conservation of sequences flanking microsatellite repeat motifs and the utility of heterologous PCR primers for analyses in closely related taxa was tested using 10 salmonid **species** from four genera. Nearly all microsatellite primers produce amplification products in **multiple species**, suggesting broad application in salmonid research. The utility of these loci for population genetic studies was tested using individuals (N = 83) from three spawning populations of chinook salmon (Oncorhynchus tshawytscha) from the Yukon River. Yukon Territories. Twelve of 16 loci screened were polymorphic (mean heterozygosity = 0.254). Genetic distance estimates between populations were concordant with results from a previous allozyme survey of these same populations. Discussions of the utility of microsatellite markers in salmonid population genetic research are presented in light of recently described statistical methodologies based on mutational properties and interallelic differences in repeat score.

L8 ANSWER 5 OF 57 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:574399 BIOSIS
DN PREV199799289080
TI Steroid sulfotransferases.
AU Luu-The, V. (1); Bernier, F.; Dufort, I.
CS (1) MRC Group Molecular Endocrinol., CHUL Res. Cent., Laurier Blvd., PQ G1V 4G2 Canada
SO Journal of Endocrinology, (1996) Vol. 150, No. SUPPL., pp. S87-S97.
ISSN: 0022-0795.
DT Article
LA English
AB Human dehydroepiandrosterone sulfotransferase (DHEA-ST) catalyzes the sulfonation of DHEA, cholesterol, pregnenolone as well as androsterone. RNA blot analysis shows two DHEA-ST mRNA **species** of 1.3 and 1.8 kb that are expressed similarly in liver and adrenals. To determine whether the form expressed in adrenals is distinct or identical with the

one expressed in liver, we have cloned and sequenced the 1.8 kb DHEA-ST **cDNA** from human adrenal **cDNA library**. Except for one nucleotide difference, the human adrenal and Ever DHEA-ST **cDNAs** are identical. Using expression vectors containing the chloramphenicol acetyltransferase (CAT) reporter gene ligated to various fragments of the DHEA-ST gene promoter, we have shown that DHEA-ST gene promoter activity is stimulated by estradiol (E-2). The E-2 stimulation is inhibited by the anti-estrogen EM-139. In contrast to human DHEA-ST, guinea pig hydroxysteroid sulfotransferases show high substrate- and stereo-selectivity. We have cloned a chiral-specific pregnenolone sulfotransferase (PREG-ST) which catalyzes mainly the transformation of pregnenolone to pregnenolone sulfate. Estrogen sulfotransferase catalyzes the conversion of estrone and estradiol to their inactive sulfated forms and could thus play a major role in the control of estrogen levels in target tissues. Recently, using a probe derived from bovine estrogen sulfotransferase, we have cloned a **cDNA** and gene that we first named human estrogen sulfotransferase (hEST) since the expressed enzyme is able to transform estrone to estrone sulfate. Actually, the Hugo nomenclature committee named this gene STM gene because it also codes for monoamine-sulfating phenolsulfotransferase (M-PST). hEST1 possesses the same coding and 3'-untranslated region as human brain aryl sulfotransferase (HAST) and M-PST, but different 5'-noncoding region. Analysis of hEST1 gene sequence indicates that hEST1 and HAST3 or M-PST mRNA **species** are transcribed from a single hEST1 gene by alternative promoters using two separate exon I, named exon Ia and exon Ib. We also described the identification of a third mRNA **species** (M-PST-gamma) issued from the STM gene and the characterization of the structure of the phenol-sulfating phenolsulfotransferase (STP) gene that is highly homologous to the STM gene. Similar to STM, the STP gene generates **multiple** m-RNA **species** that differ only in the 5'-untranslated sequence.

L8 ANSWER 6 OF 57 MEDLINE DUPLICATE 3
AN 95247712 MEDLINE
DN 95247712
TI Characterization of mouse and human GTP cyclohydrolase I genes. Mutations in patients with GTP cyclohydrolase I deficiency.
AU Ichinose H; Ohye T; Matsuda Y; Hori T; Blau N; Burlina A; Rouse B; Matalon R; Fujita K; Nagatsu T
CS Institute for Comprehensive Medical Science, Fujita Health University, Aichi, Japan..
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Apr 28) 270 (17) 10062-71. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
OS GENBANK-D38601; GENBANK-D38602; GENBANK-D38603; GENBANK-U19256; GENBANK-U19257; GENBANK-U19258; GENBANK-U19259
EM 199508
AB GTP cyclohydrolase I is the first and rate-limiting enzyme for the biosynthesis of tetrahydrobiopterin in mammals. Previously, we reported three **species** of human GTP cyclohydrolase I **cDNA** in a human liver **cDNA library** (Togari, A., Ichinose, H., Matsumoto, S., Fujita, K., and Nagatsu, T. (1992) Biochem. Biophys. Res. Commun. 187, 359-365). Furthermore, very recently, we found that the GTP cyclohydrolase I gene is causative for hereditary progressive dystonia

with marked diurnal fluctuation, also known as DOPA-responsive dystonia (Ichinose, H., Ohye, T., Takahashi, E., Seki, N., Hori, T., Segawa, M., Nomura, Y., Endo, K., Tanaka, H., Tsuji, S., Fujita, K., and Nagatsu, T. (1994) Nature Genetics 8, 236-242). To clarify the mechanisms that regulate transcription of the GTP cyclohydrolase I gene and to generate **multiple species** of mRNA, we isolated **genomic** DNA clones for the human and mouse GTP cyclohydrolase I genes. Structural analysis of the isolated clones revealed that the GTP cyclohydrolase I gene is encoded by a single copy gene and is composed of six exons spanning approximately 30 kilobases. We sequenced all exon/intron boundaries of the human and mouse genes. Structural analysis also demonstrated that the heterogeneity of GTP cyclohydrolase I mRNA is caused by an alternative usage of the splicing acceptor site at the sixth exon. The transcription start site of the mouse GTP cyclohydrolase I gene and the 5'-flanking sequences of the mouse and human genes were determined. We performed regional mapping of the mouse gene by fluorescence in situ hybridization, and the mouse GTP cyclohydrolase I gene was assigned to region C2-3 of mouse chromosome 14. We identified missense mutations in patients with GTP cyclohydrolase I deficiency and expressed mutated enzymes in Escherichia coli to confirm alterations in the enzyme activity.

L8 ANSWER 7 OF 57 CAPLUS COPYRIGHT 1999 ACS
AN 1994:531123 CAPLUS
DN 121:131123
TI Molecular cloning and expression of collagenase-3, a novel human matrix metalloproteinase produced by breast carcinomas
AU Freije, Jose M. P.; Diez-Itza, Irene; Balbin, Milagros; Sanchez, Luis M.; Blasco, Rafael; Tolivia, Jorge; Lopez-Otin, Carlos
CS Dep. Biol. func., Univ. Oviedo, Oviedo, 33006, Spain
SO J. Biol. Chem. (1994), 269(24), 16766-73
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB A **cDNA** coding for a new human matrix metalloproteinase (MMP) has been cloned from a **cDNA library** derived from a breast tumor. The isolated **cDNA** contains an open reading frame coding for a polypeptide of 471 amino acids. The predicted protein sequence displays extensive similarity to the previously known MMPs and presents all the structural features characteristic of the members of this protein family, including the well conserved PRCGXPD motif, involved in the latency of the enzyme and the zinc-binding domain (HEXGHXXXXXHS). In addn., this novel human MMP contains in its amino acid sequence several residues specific to the collagenase subfamily (Tyr-214, Asp-235, and Gly-237) and lacks the 9-residue insertion present in the stromelysins. According to these structural characteristics, the MMP described herein has been tentatively called collagenase-3, since it represents the third member of this subfamily, composed at present of fibroblast and neutrophil collagenases. The collagenase-3 **cDNA** was expressed in a vaccinia virus system, and the recombinant protein was able to degrade fibrillar collagens, providing support to the hypothesis that the isolated **cDNA** codes for an authentic collagenase. Northern blot anal. of RNA from normal and pathol. tissues demonstrated the existence in breast tumors of three different mRNA **species**, which seem to be the result of the utilization of different polyadenylation sites present in the 3'-noncoding region of the gene. By contrast, no collagenase-3 mRNA

was detected either by Northern blot or RNA polymerase chain reaction anal. with RNA from other human tissues, including normal breast, mammary fibroadenomas, liver, placenta, ovary, uterus, prostate, and parotid gland. On the basis of the increased expression of collagenase-3 in breast carcinomas and the absence of detectable expression in normal tissues a possible role for this metalloproteinase in the tumoral process is proposed.

L8 ANSWER 8 OF 57 MEDLINE
AN 94307732 MEDLINE
DN 94307732
TI Human and rodent OMP genes: conservation of structural and regulatory motifs and cellular localization.
AU Buiakova O I; Krishna N S; Getchell T V; Margolis F L
CS Roche Institute of Molecular Biology, Nutley, New Jersey 07110..
NC NIDCD 00159
SO GENOMICS, (1994 Apr) 20 (3) 452-62.
Journal code: GEN. ISSN: 0888-7543.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U01212; GENBANK-U01213
EM 199410
AB Immunocytochemical analysis has demonstrated that expression of the olfactory marker protein (OMP) is highly restricted to mature olfactory receptor neurons in virtually all vertebrate **species** from fish to man. We have now cloned the OMP gene from human and mouse and demonstrated conservation of gene structure, protein sequence, and Olf-1 and upstream binding region (UBE) regulatory domains. The OMP gene in all **species** studied lacks canonical TATA and CAAT motifs and introns. The deduced protein sequence is 88.4% identical between mouse and human, and most of the differences observed are conservative changes. The proximal Olf-1 binding sites differ by two purine-purine replacements and effectively cross-compete in mobility shift assays. The distal Olf-1 binding site is also highly conserved in terms of both sequence and binding activity. The availability of sequence from **multiple species** has permitted us to determine that the UBE site has close similarity to motifs that bind members of the NF-1 family of transcription factors. Gel mobility shift assays confirm this prediction, providing additional insight into mechanisms that may participate in the stringent regulation of the expression of this neuronal-specific protein. Furthermore, we demonstrate the in situ localization of OMP mRNA in human olfactory neuro-epithelium and its colocalization to immunocytochemically identified human olfactory receptor neurons.

L8 ANSWER 9 OF 57 CAPLUS COPYRIGHT 1999 ACS
AN 1994:3470 CAPLUS
DN 120:3470
TI Molecular cloning and deduced amino acid sequences of the .gamma.-subunits of rat and monkey NAD+-isocitrate dehydrogenases
AU Nichols, Benjamin J.; Hall, Len; Perry, Anthony C. F.; Denton, Richard M.
CS Sch. Med. Sci., Univ. Bristol, Bristol, BS8 1TD, UK
SO Biochem. J. (1993), 295(2), 347-50
CODEN: BIJOAK; ISSN: 0306-3275
DT Journal
LA English
AB A 600 bp **cDNA** fragment encoding part of the .gamma.-subunit of

pig heart NAD+-isocitrate dehydrogenase (ICDH.gamma.) was amplified by PCR using redundant oligonucleotide primers based on partial peptide sequence data [Huang and Colman (1990) Biochem. 29, 8266-8273]. This PCR fragment was then used as a probe to isolate clones encoding the complete mature forms of the .gamma.-subunit from rat epididymis and monkey testis **cDNA libraries**. Comparison of the deduced amino acid sequences of the rat and monkey subunits and the partial sequence of the pig heart enzyme revealed a remarkably high level of sequence identity. The relationship between the deduced amino acid sequences of the NAD+-ICDH .gamma.-subunits and those of nonmammalian NAD+- and NADP+-ICDH subunits is discussed.

L8 ANSWER 10 OF 57 CAPLUS COPYRIGHT 1999 ACS
AN 1994:50992 CAPLUS
DN 120:50992
TI Unique hexokinase messenger ribonucleic acids lacking the porin-binding domain are developmentally expressed in mouse spermatogenic cells
AU Mori, Chisato; Welch, J. E.; Fulcher, K. D.; O'Brien, D. A.; Eddy, E. M.
CS Gamete Biol. Sect., Natl. Inst. Environ. Health Sci., Research Triangle Park, NC, 27709, USA
SO Biol. Reprod. (1993), 49(2), 191-203
CODEN: BIREBV; ISSN: 0006-3363
DT Journal
LA English
AB The authors have identified **cDNAs** representing 3 hexokinase mRNAs (Hk1-sa, Hk1-sb, Hk1-s.c.) by screening mouse spermatogenic cell **cDNA libraries** with a mouse hepatoma cell line hexokinase (Hk1) **cDNA**. Although all 3 **cDNAs** show 99% identity to the somatic Hk1 **cDNA** sequence throughout most of their coding region, they differ from the sequence at the 5' end. They contain a common spermatogenic cell-specific sequence and a sequence unique to each **cDNA** immediately 5' to the common domain. However, they lack the porin-binding domain (PBD) present in this region of Hk1, used for binding to a pore-forming protein in the outer mitochondrial membrane. These observations appear to support a model proposed by others for hexokinase gene evolution in mammals. In addn., Hk1-sb has an internal sequence that is not present in Hk1, Hk1-sa, or Hk1-s.c. Moreover, Hk1-sa and Hk1-sb transcripts are developmentally expressed in mouse spermatogenic cells. Hk1-sa mRNA is first expressed during meiosis and continues to be present in postmeiotic germ cells, whereas the more abundant Hk1-sb mRNA is detected only in postmeiotic germ cells. Apparently, enzymes encoded by Hk1-sa, Hk1-sb, and Hk1-s.c. are present only in spermatogenic cells.

L8 ANSWER 11 OF 57 MEDLINE DUPLICATE 4
AN 93240983 MEDLINE
DN 93240983
TI **Multiple** mRNA **species** of choline acetyltransferase from rat spinal cord.
AU Kengaku M; Misawa H; Deguchi T
CS Department of Molecular Neurobiology, Tokyo Metropolitan Institute for Neuroscience, Japan.
SO BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1993 Apr) 18 (1-2) 71-6.
Journal code: MBR. ISSN: 0169-328X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
OS GENBANK-S59202; GENBANK-S59203; GENBANK-S59209; GENBANK-S59244; GENBANK-S62176; GENBANK-S62178; GENBANK-S62179; GENBANK-S62182; GENBANK-S62184; GENBANK-X59067
EM 199307
AB A **cDNA library** directed by a specific primer was constructed from the rat spinal cord and screened with 32P-labeled rat choline acetyltransferase **cDNA** which was recently isolated in this laboratory. Sequence analysis of 29 clones indicated that there are four types of **cDNA** (R1-, R2-, N1- and M-types). The nucleotide sequences in these **cDNAs** were identical in the coding region and the first 38 bp of the 5'-noncoding region, but differed in the 5'-noncoding region upstream of -38 bp. The R1-type was identical to the **cDNA** previously cloned from the rat spinal cord. The M and N1-type **cDNAs** both had sequences homologous to that of the **cDNA** previously obtained from the mouse spinal cord. Polymerase chain reaction analysis confirmed the presence of these 4 types of mRNA and found another type (N2-type) of transcript. The numbers of **cDNA** clones isolated and the relative amounts of polymerase chain reaction products for each type of mRNA suggested that the most abundant transcript was M-type. Sequencing of the **genomic** clone containing the 5'-region of choline acetyltransferase mRNA revealed that these five types of mRNA **species** were transcribed from three different promoter regions and produced by differential splicing of the 5'-noncoding exons.

L8 ANSWER 12 OF 57 MEDLINE DUPLICATE 5
AN 93077559 MEDLINE
DN 93077559
TI Molecular cloning and functional expression of **cDNA** encoding a mammalian inorganic pyrophosphatase.
AU Yang Z; Wensel T G
CS Verna and Marrs McLean Department of Biochemistry, Baylor College of Medicine, Houston, Texas 77030.
NC EY07981 (NEI)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1992 Dec 5) 267 (34) 24641-7. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-M95283; GENBANK-D10517; GENBANK-D10518; GENBANK-D10519; GENBANK-D10520; GENBANK-D12749; GENBANK-D12750; GENBANK-D12751; GENBANK-D12752; GENBANK-D12753
EM 199303
AB Extracts of soluble proteins from bovine retina contain **multiple species** of inorganic pyrophosphatase (PPase) that can be resolved by hydroxylapatite or ion exchange chromatography. We have purified one of these isoforms by a combination of chromatography and electrophoresis under denaturing conditions and have partially sequenced four peptides generated from it by CNBr digestion. This sequence information was used to clone PPase **cDNA** from a retinal **cDNA library** . Of five **cDNA** inserts, three were 1.3 kilobase pairs in length and two of these contained a complete open reading frame that was 867 base pairs long and encoded a 289-amino acid protein of 33 kDa. The deduced amino acid sequence is 49.5% identical to that of PPase from Saccharomyces

cerevisiae, and contains identical amino acid residues at all of the positions previously identified as essential for catalytic activity in that enzyme. When the bovine PPase **cDNA** was expressed in Escherichia coli, catalytically active PPase was produced that comigrated with bovine retinal PPase in a nondenaturing gel and was clearly distinguishable from the host PPase. Northern analysis of poly(A)+ RNA from human, canine, and bovine retinas revealed that each contained a single major band of 1.4 kilobases that hybridized strongly with a pyrophosphatase **cDNA** probe. Southern analysis of bovine **genomic** DNA was consistent with the existence of one PPase gene. Thus, the multiple forms separated by chromatography may be derived from a common precursor or from mRNAs of very similar size.

L8 ANSWER 13 OF 57 MEDLINE DUPLICATE 6
AN 93078769 MEDLINE
DN 93078769
TI Sequence of **cDNA** comprising the human pur gene and sequence-specific single-stranded-DNA-binding properties of the encoded protein.
AU Bergemann A D; Ma Z W; Johnson E M
CS Department of Pathology, Mount Sinai Medical School, New York, New York 10029.
NC CA55219 (NCI)
SO MOLECULAR AND CELLULAR BIOLOGY, (1992 Dec) 12 (12) 5673-82. Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-M96684
EM 199303
AB The human Pur factor binds strongly to a sequence element repeated within zones of initiation of DNA replication in several eukaryotic cells. The protein binds preferentially to the purine-rich single strand of this element, PUR. We report here the cloning and sequencing of a **cDNA** encoding a protein with strong affinity for the PUR element. Analysis with a series of mutated oligonucleotides defines a minimal single-stranded DNA Pur-binding element. The expressed Pur open reading frame encodes a protein of 322 amino acids. This protein, Pur alpha, contains three repeats of a consensus motif of 23 amino acids and two repeats of a second consensus motif of 26 amino acids. Near its carboxy terminus, the protein possesses an amphipathic alpha-helix and a glutamine-rich domain. The repeat region of Pur **cDNA** is homologous to **multiple** mRNA **species** in each of several human cell lines and tissues. The HeLa **cDNA library** also includes a clone encoding a related gene, Pur beta, containing a version of the 23-amino-acid consensus motif similar, but not identical, to those in Pur alpha. Results indicate a novel type of modular protein with capacity to bind repeated elements in single-stranded DNA.

L8 ANSWER 14 OF 57 MEDLINE
AN 92319622 MEDLINE
DN 92319622
TI **Multiple** mRNA **species** generated by alternate polyadenylation from the rat manganese superoxide dismutase gene.

AU Hurt J; Hsu J L; Dougall W C; Visner G A; Burr I M; Nick H S
CS Department of Biochemistry and Molecular Biology, College of Medicine, University of Florida, Gainesville 32610..
NC RO1-HL39593 (NHLBI)
SO NUCLEIC ACIDS RESEARCH, (1992 Jun 25) 20 (12) 2985-90.
Journal code: O8L. ISSN: 0305-1048.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199210
AB The mitochondrial enzyme, manganese superoxide dismutase (MnSOD) is an integral component of the cell's defense against superoxide-mediated cellular damage. We have isolated and characterized four **cDNA** clones and the structural gene for rat MnSOD. Northern analyses using MnSOD **cDNA** probes detected at least five mRNAs in all tissues and cell types examined. Southern and Northern analysis using a 3' non-coding sequence probe, common to all the **cDNAs**, showed hybridization only to **genomic** restriction fragments that correspond to our **genomic** clone and the five MnSOD mRNAs. These data demonstrate that all of the rat MnSOD transcripts are derived from a single functional gene. Primer extension data indicate that transcription initiation is clustered within a few bases. Northern analysis using intron probes demonstrates that all five transcripts are fully processed. Northern analysis using **cDNA** and **genomic** probes from sequences progressively 3' to the end of the coding sequence indicates that size heterogeneity in the MnSOD transcripts results from variations in the length of the 3' non-coding sequence. From this data and the location of potential polyadenylation signals near the expected sites of transcript termination, we conclude that the existence of **multiple** MnSOD mRNA **species** originate as the result of alternate polyadenylation.

L8 ANSWER 15 OF 57 MEDLINE DUPLICATE 7
AN 92114192 MEDLINE
DN 92114192
TI The third subunit of protein phosphatase 2A (PP2A), a 55-kilodalton protein which is apparently substituted for by T antigens in complexes with the 36- and 63-kilodalton PP2A subunits, bears little resemblance to T antigens.
AU Pallas D C; Weller W; Jaspers S; Miller T B; Lane W S; Roberts T M
CS Division of Cellular and Molecular Biology, Dana-Farber Cancer Institute, Boston, Massachusetts..
NC CA30002 (NCI)
CA45285 (NCI)
DK 18269 (NIDDK)
SO JOURNAL OF VIROLOGY, (1992 Feb) 66 (2) 886-93.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-M83297; GENBANK-M83298
EM 199204
AB The small and middle T (tumor) antigens of polyomavirus have been shown previously to associate with the 36-kDa catalytic subunit and the 63-kDa regulatory subunit of protein phosphatase type 2A, apparently substituting for a normal third 55-kDa regulatory subunit (D.C. Pallas, L.K. Shahrik,

B.L. Martin, S. Jaspers, T.B. Miller, D.L. Brautigan, and T.M. Roberts, Cell 60:167-176, 1990). To facilitate a comparison of the normal regulatory subunit and T antigens, we isolated a 2.14-kb **cDNA** clone encoding this 55-kDa subunit from a rat liver **library**. Using a probe from the coding region of this gene, we detected a major 2.4-kb mRNA transcript in liver and muscle RNAs. The 55-kDa protein phosphatase 2A subunit purified from rat skeletal muscle generates **multiple species** when analyzed on two-dimensional gels. Transcription and translation of the clone in vitro produced a full-length protein that comigrated precisely on two-dimensional gels with three of these **species**, indicating that the 55-kDa protein is apparently modified similarly in vivo and in reticulocyte lysates. Additional **species** in the purified preparation were not found in the translate, suggesting that there are probably two or more isoforms of this protein in rat muscle. Somewhat surprisingly, there was no clear homology with T-antigen amino acid sequences.

L8 ANSWER 16 OF 57 CAPLUS COPYRIGHT 1999 ACS
AN 1992:525766 CAPLUS
DN 117:125766
TI Expression cloning of a rat B2 bradykinin receptor
AU McEachern, Adrienne E.; Shelton, Earl R.; Bhakta, Sunil; Obernolte, Rena; Bach, Chinh; Zuppan, Patricia; Fujisaki, Jill; Aldrich, Richard W.; Jarnagin, Kurt
CS Howard Hughes Med. Inst., Stanford Univ., Stanford, CA, 94305, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1991), 88(17), 7724-8
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB A **cDNA** encoding a functional bradykinin receptor was isolated from a rat uterus **library** by a clonal selection strategy using Xenopus laevis oocytes to assay for expression of bradykinin responses. The predicted protein is homologous to the 7 transmembrane G protein-coupled superfamily of receptors. Bradykinin and its analogs stimulate a Cl- current in oocytes expressing the receptor with the rank order of potency: bradykinin .apprxeq. Lys-bradykinin > [Tyr8]-bradykinin >> [Phe6]bradykinin. This is the rank order of potency obsd. for these compds. in competitive binding assays on sol. receptor from rat uterus. Des-Arg9-bradykinin (10 .mu.M) elicits no response when applied to oocytes expressing the receptor; thus, the **cDNA** encodes a B2 type bradykinin receptor. [Thi5,8,DPhe7]bradykinin, where Thi is .beta.-(2-thienyl)-alanine, is a very weak partial agonist and inhibits the bradykinin-mediated ion flux, suggesting the **cDNA** encodes a smooth muscle, rather than a neuronal, B2 receptor subtype. Receptor message has a distribution consistent with previous reports of bradykinin function and/or binding in several tissues and is found in rat uterus, vas deferens, kidney, lung, heart, ileum, testis, and brain. Receptor subtypes are a possibility because several tissues contain 2 or 3 message **species** (4.0, 5.7, and 6.5 kilobases). Southern blot high-stringency anal. demonstrated that the rat, guinea pig, and human **genomes** contain a single gene. As bradykinin is a key mediator of pain, knowledge of the primary structure of this receptor will allow a mol. understanding of the receptor and aid the design of antagonists for pain relief.

L8 ANSWER 17 OF 57 CAPLUS COPYRIGHT 1999 ACS

AN 1991:507454 CAPLUS
DN 115:107454
TI An additional promoter functions in the human aldolase A gene, but not in rat
AU Mukai, Tsunehiro; Arai, Yuji; Yatsuki, Hitomi; Joh, Keiichiro; Hori, Katsuji
CS Res. Inst., Natl. Cardiovasc. Cent., Osaka, 565, Japan
SO Eur. J. Biochem. (1991), 195(3), 781-7
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB The aldolase A gene was isolated from a human DNA **library**, mapped, and sequenced. This gene comprises 12 exons and spans 6.5 kb. From the **genomic** DNA sequence and from the previous sequence anal. of the **cDNA**, it was revealed that the first exon L1 and the second exon encode the 5' non-coding sequence of mRNA L1, whereas the third and forth exons (corresponding to exons M and L2) encode different mRNA, mRNA M and L2, resp.; the following 8 exons (exons 5-12) are shared commonly by all the mRNA **species**. These results indicate that the mRNA **species** are generated from a single aldolase A gene from one of exons L1, M, or L2, in addn. to exons 5-12, and also that the usage of a leader exon is similar but clearly distinct from that of rat aldolase A gene previously (Joh, K., et al., 1986). By comparing the promoter regions in the human and rat aldolase A genes, similar sequences were found in the rat **genome** corresponding to those of the human L1, M and L2 promoter. However, no transcripts starting from sequences corresponding to the human L1 promoter were found in the rat **genome**, although the products corresponding to human M and L2 were detected. Apparently, the L1 promoter was either acquired by the human **genome** or deleted from the rat **genome** after human and rat diverged during evolution.

L8 ANSWER 18 OF 57 MEDLINE DUPLICATE 8
AN 92037619 MEDLINE
DN 92037619
TI **Multiple** mRNA **species** code for two non-allelic forms of ovine alpha s2-casein.
AU Boisnard M; Hue D; Bouniol C; Mercier J C; Gaye P
CS Unite d'Endocrinologie moleculaire, Institut National de la Recherche Agronomique, Jouy-en-Josas, France..
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1991 Nov 1) 201 (3) 633-41.
Journal code: EMZ. ISSN: 0014-2956.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-X03238; GENBANK-S64844; GENBANK-S64846; GENBANK-S64848; GENBANK-X57951; GENBANK-X56257; GENBANK-M60272; GENBANK-M60273; GENBANK-M60352; GENBANK-M60353; GENBANK-M60354
EM 199202
AB The two non-allelic forms of alpha s2-casein, occurring in ovine milk, differ by an internal deletion of nine amino acid residues, including both cysteine residues at positions 34 and 42 in the mature chain. Sequencing of several alpha s2-casein **cDNA**, isolated from the mammary **cDNA library** of a single lactating ewe, showed three new types which differed from that previously studied. In addition to the expected deletion of codons +34 to +42 affecting 30-40% of mRNA, another structural difference involving an internal stretch of 44 nucleotides in the 5' untranslated region, was found. S1-nuclease protection assays

confirmed the existence of several types of the relevant mRNA and sequencing of in-vitro-amplified **genomic** DNA demonstrated the presence of the 44-nucleotide stretch in the alpha s2-casein transcriptional unit, thus ruling out the possibility of a cloning artefact. The different alpha s2-casein mRNA, four in terms of deletion and two in terms of nucleotide substitutions for a given ewe, can be readily explained by partial exon skipping and allelic differences, respectively. This assumption is well supported by the following observations: 5' and 3' ends of both deleted DNA fragments are similar to those of exons; sequences neighbouring the 44-nucleotide stretch of the **genomic** DNA perfectly match consensus sequences described for 3' and 5' ends of introns; the rather simple patterns observed on Southern blots of different enzymatic digests of **genomic** DNA strongly suggest the occurrence of only 1 copy alpha s2-casein gene/haploid **genome**. During the course of evolution, the alpha s2-casein-encoding gene has undergone many mutations and some of them might have occurred in regions corresponding to consensus splicing regions of the pre-mRNA. Thus, complete skipping of some exons might be responsible for the shorter sizes of rat and mouse alpha s2-casein mRNA. If so, the overall organization of the alpha s2-casein gene in the different **species** might be more similar than expected from structural comparisons of the cognate mRNA or caseins.

L8 ANSWER 19 OF 57 CAPLUS COPYRIGHT 1999 ACS
AN 1991:671763 CAPLUS
DN 115:271763
TI The tat protein of equine infectious anemia virus is encoded by at least three types of transcripts
AU Noiman, Silvia; Yaniv, Abraham; Tsach, Tsvia; Miki, Toru; Tronick, Steven R.; Gazit, Arnona
CS Sackler Sch. Med., Tel Aviv Univ., Tel Aviv-Jaffa, 69978, Israel
SO Virology (1991), 184(2), 521-30
CODEN: VIRLAX; ISSN: 0042-6822
DT Journal
LA English
AB Nucleotide sequence anal. of a **cDNA library** of equine infectious anemia virus (EIAV)-infected canine cells established a complex pattern of gene expression, characterized by alternatively spliced polycistronic transcripts. The EIAV tat gene product was shown to be encoded by .gtoreq.3 **species** of mRNA which differed in their ability to trans-activate the EIAV LTR upon expression in canine cells. The most active **cDNA** was monocistronic, consisting of 3 exons. The most abundant **cDNA** in the **library** contained 4 exons and was identical to a polycistronic transcript previously described (S. Noiman et al., 1990) which contains open frames for Tat, putative Rev, and truncated transmembrane proteins. Products consistent in size with those predicted for these last 2 proteins could be detected in in vitro translation expts. The third Tat message, another 4-exon form, also potentially encodes an N-terminally truncated transmembrane protein. In vitro mutagenesis expts. and anal. of subgenomic and partial **cDNA** clones confirmed and extended previous findings that S1 sequences are essential for trans-activation and that Tat translation initiates at a non-AUG codon either in the full-length Tat message or in the **genomic** S1 open reading frame. The Tat protein (8 kDa) was detected in cells transfected with a Tat **cDNA** construct and in canine cells persistently infected with EIAV. The Tat activity of

polycistronic mRNAs was lower than that of the monocistronic form, suggesting that the expression of the EIAV transactivator may be subject to several levels of posttranscriptional control.

L8 ANSWER 20 OF 57 CAPLUS COPYRIGHT 1999 ACS
AN 1993:17237 CAPLUS
DN 118:17237
TI Molecular cloning of human lysyl oxidase and assignment of the gene to chromosome 5q23.3-31.2
AU Hamalainen, Eija Riitta; Jones, Tania A.; Sheer, Denise; Taskinen, Kirsi; Pihlajaniemi, Taina; Kivirikko, Kari I.
CS Biocent., Univ. Oulu, Oulu, SF-90220, Finland
SO Genomics (1991), 11(3), 508-16
CODEN: GNMCEP; ISSN: 0888-7543
DT Journal
LA English
AB Lysyl oxidase (EC 1.4.3.13) initiates the crosslinking of collagens and elastin by catalyzing oxidative deamination of the .epsilon.-amino group in certain lysine and hydroxylysine residues. This report describes the isolation and characterization of **cDNA** clones for the enzyme from human placenta and rat aorta .lambda.gt11 **cDNA libraries**. A **cDNA** clone for human lysyl oxidase covers all the coding sequences, 230 nucleotides of the 5' and 299 nucleotides of the 3' untranslated sequences, including a poly(A) tail of 23 nucleotides. This **cDNA** encodes a polypeptide of 417 amino acid residues, including a signal peptide of 21 amino acids. Sequencing of 2 rat lysyl oxidase **cDNA** clones indicated 6 differences between the present and the previously published sequence for the rat enzyme (Trackman, P. C., et al. 1990), resulting in frameshifts in the translated sequence. The human lysyl oxidase sequence was found to be 78% identical to the revised rat sequence at the nucleotide level and 84% identical at the amino acid level, with the degree of identity unevenly distributed between various regions of the coded polypeptide. Northern blot anal. of human skin fibroblast RNA indicated that the human lysyl oxidase **cDNA** hybridizes to at least 4 mRNA **species**; their sizes are about 5.5, 4.3, 2.4, and 2.0 kb. Anal. of a panel of 25 human .times. hamster cell hybrids by Southern blotting mapped the human lysyl oxidase gene to chromosome 5, and in situ hybridization mapped it to 5q23.3-31.2. This assignment excludes primary defects in this gene as causes of the deficiency in lysyl oxidase activity and enzyme protein which are found in 2 X-linked recessively inherited disorders, the Menkes syndrome and the type IX variant of the Ehlers-Danlos syndrome.

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L2         3494 LI AND REVIEW

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L3           64 L1 AND REVIEW

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L5   ANSWER 1 OF 46  CAPLUS  COPYRIGHT 1999 ACS
AN   1996:470702  CAPLUS
DN   125:137270
TI   Genes, enzymes and secondary metabolites in industrial
     microorganisms: the 1995 Thom Award Lecture
AU   Beppu, T.
CS   Dep. Applied Biological Sci., Nihon Univ., Kanagawa, 252, Japan
SO   J. Ind. Microbiol. (1996), 16(6), 360-363
     CODEN: JIMIE7; ISSN: 0169-4146
DT   Journal; General Review
LA   English
AB   A review with 19 refs.  Apparently contrasting approaches, i.e.
     genetic engineering and screening of new microorganisms, play essential
     complementary roles to develop current industrial microbiol.  Three
     topics, prodn. and modification of milk-clotting proteinases by genetic
     engineering, hormonal control of secondary metab. in
     streptomycetes, and screening of bioactive metabolites, are introduced as
     cases of such a hybrid approach, while symbiotic microorganisms are
     discussed as an example of the vast terra incognita still remaining for
     the future microbiol.

L5   ANSWER 2 OF 46  BIOSIS  COPYRIGHT 1999 BIOSIS
AN   1996:386059  BIOSIS
DN   PREV199699108415
TI   Lignins and lignification: Recent biochemical and biotechnological
     developments.
AU   Boudet, Alain M. (1); Goffner, Deborah P.; Grima-Pettenati, Jacqueline
CS   (1) Signaux Messages Cellulaires Chez les Vegetaux, UMR 5546, CNRS, Univ.
     Paul-Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex France
SO   Comptes Rendus de l'Academie des Sciences Serie III Sciences de la Vie,
     (1996) Vol. 319, No. 4, pp. 317-331.
     ISSN: 0764-4469.
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DT General Review
LA English; French
SL English; French
AB As a result of recent advances in molecular biology, the lignin biosynthetic pathway has been critically re-examined and appears more complex than originally assumed. The existence of alternative pathways, on one hand, and the presence of specific isoforms for the "classical pathway" on the other, may be implicated in the regulation of the monomeric composition of lignins. Indeed the chemical heterogeneity of lignins that exists between species, tissues (within a given individual), and as a function of various physiological conditions appears to be under strict control. Differential partitioning of assimilated, photosynthetic carbon into lignins (as reflected in the varying lignin content among species) is likely to involve competition between primary and **secondary metabolism**. In this context, a coordinated activation of key enzymes of primary, pre-aromatic, and secondary phenolic metabolism must be an important control mechanism. Beyond the characterization of lignification **genes**, it is now possible to demonstrate, via chimeric **gene** expression, the tissue specific nature of their promoter activity. The identification of promoter regions conferring this specificity is currently underway. Lignins synthesized de novo in response to stress (elicitation, wounding) not only have an altered monomer composition as compared to constitutive lignins but they also appear to be under strict spatial control. On a fundamental level lignification often accompanies programmed cell death, a domaine of growing interest in the field of developmental biology. Finally, this **review** highlights recent advances aimed at modifying lignification by genetic engineering and describes potential biotechnological applications.

L5 ANSWER 3 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1996:292653 CAPLUS
DN 124:337780
TI Modifying resistance to plant-pathogenic fungi
AU Pierpoint, W. S.; Hargreaves, J. A.; Shewry, P. R.
CS IACR-Rothamsted, UK
SO Genet. Eng. Crop Plants Resist. Pests Dis. (1996), 66-83. Editor(s): Pierpoint, W. S.; Shewry, P. R. Publisher: British Crop Protection Council, Farnham, UK.
CODEN: 62UKAG
DT Conference; General Review
LA English
AB A discussion with many refs. on the title as to the isolation of plant r-**genes**, resistance based on antifungal proteins, and resistance based on the genetic manipulation of **secondary metab**.

L5 ANSWER 4 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1996:721128 CAPLUS
DN 126:15192
TI Metabolic engineering: prospects for crop improvement through the genetic manipulation of phenylpropanoid biosynthesis and defense responses - a **review**
AU Dixon, Richard A.; Lamb, Chris J.; Masoud, Sameer; Sewalt, Vincent J. H.; Paiva, Nancy L.
CS Plant Biology Division, Samuel Roberts Noble Foundation, P.O. Box 2180, Ardmore, OK, 73402, USA
SO Gene (1996), 179(1), 61-71
CODEN: GENED6; ISSN: 0378-1119

PB Elsevier
DT Journal; General Review
LA English
AB A **review** with 76 refs. In leguminous plants such as the forage legume alfalfa, products of the phenylpropanoid pathway of **secondary metab**. are involved in interactions with beneficial microorganisms (flavonoid inducers of the Rhizobium symbiosis), and in defense against pathogens (isoflavonoid phytoalexins). In addn., the phenylpropane polymer lignin is a major structural component of secondary vascular tissue and fibers in higher plants. The recent isolation of **genes** encoding key enzymes of the various phenylpropanoid branch pathways opens up the possibility of engineering important crop plants such as alfalfa for: (a) improved forage digestibility, by modification of lignin compn. and/or content; (b) increased or broader-spectrum disease resistance, by introducing novel phytoalexins or structural variants of the naturally occurring phytoalexins, or by modifying expression of transcriptional regulators of phytoalexin pathways; and (c) enhanced nodulation efficiency, by engineering over-prodn. of flavonoid nod **gene** inducers. The basic biochem. and mol. biol. underlying these strategies is briefly reviewed, and recent progress with transgenic plants summarized. The potential importance of metabolic compartmentation for attempts to engineer phenylpropanoid biosynthetic pathways is also discussed. Over-expression of an alfalfa glucanase-encoding **gene** confers significant protection against Phytophthora in alfalfa, possibly via indirect effects on phenylpropanoid metab.

L5 ANSWER 5 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1996:252973 CAPLUS
DN 124:283800
TI Bacterial signalling involving eukaryotic-type protein kinases
AU Zhang, Cheng-Cai
CS Ecole Superieure Biotechnol. Strasbourg, Univ. Louis Pasteur Strasbourg, Illkirch, F-67400, Fr.
SO Mol. Microbiol. (1996), 20(1), 9-15
CODEN: MOMIEE; ISSN: 0950-382X
DT Journal; General Review
LA English
AB A **review** with 32 refs. Protein Ser, Thr and Tyr kinases play essential roles in signal transduction in organisms ranging from yeast to mammals, where they regulate a variety of cellular activities. During the last few years, a no. of **genes** that encode eukaryotic-type protein kinases have also been identified in four different bacterial species, suggesting that such enzymes are also widespread in prokaryotes. Although many of them have yet to be fully characterized, several studies indicate that eukaryotic-type protein kinases play important roles in regulating cellular activities of these bacteria, such as cell differentiation, pathogenicity and **secondary metab**. A model based on the possible coupling between two-component systems and eukaryotic-type protein kinases is proposed to explain the function of eukaryotic-type protein kinases in bacterial signalling in the light of studies in bacteria, as well as in plants and yeast. These two groups of eukaryotes possess signal transduction pathways involving both two-component systems and eukaryotic protein kinases.

L5 ANSWER 6 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1996:3495 CAPLUS
DN 124:50256

TI From molecular genetics and **secondary metabolism** to molecular metabolites and secondary genetics
AU Bennett, J. W.
CS Department Cell and Molecular Biology, Tulane University, New Orleans, LA, 70118, USA
SO Can. J. Bot. (1995), 73(Suppl. 1, Sect. E-H, Fifth International Mycological Congress, Sect. E-H, 1994), S917-S924
CODEN: CJBOAW; ISSN: 0008-4026
DT Journal; General Review
LA English
AB A **review** with 64 refs. Secondary metabolites constitute a huge array of low-mol.-wt. natural products that cannot be easily defined. Largely produced by bacteria, fungi, and green plants, they tend to be synthesized after active growth has ceased in families of similar compds., often at the same time as species-specific morphol. characters become apparent. Although, in many cases, the function that the secondary metabolite performs in the producing organism is unknown, the bioactivity of these compds. has been exploited since prehistoric times as drugs, poisons, food flavoring agents, and so forth. In fungi, the polyketide family is the largest known group of secondary metabolite compds. Polyketides are synthesized from acetate by a mechanism analogous to fatty acid biosynthesis but involving changes in oxidn. level and stereochem. during the chain-elongation process. The fungal polyketide biosynthetic pathways for aflatoxin and patulin have emerged as model systems. The use of blocked mutants has been an essential part of the research approach for both pathways. Mol. methods of studying fungal secondary metabolites were first used with penicillin and cephalosporin, both of which are amino acid derived. Most of the basic mol. work on polyketides was done with streptomycete-derived compds.; however, enough fungal data are now available to compare fungal and streptomycete polyketide synthases, as well as to map the **genes** involved in a no. of polyketide pathways from both groups. The traditional dogma, derived from classical genetics, that **genes** for fungal pathways are unlinked has been overturned. In addn., cloning of structural **genes** facilitates the formation of hybrid mols., and we are on the brink of understanding certain regulatory functions.

L5 ANSWER 7 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1996:490579 CAPLUS
DN 125:137314
TI A conserved polyketide mycotoxin **gene** cluster in Aspergillus nidulans.
AU Keller, Nancy P.; Brown, Daren; Butchko, Robert A. E.; Fernandes, Mary; Kelkar, Hemant; Nesbitt, Clint; Segner, Suzanne; Bhatnagar, Deepak; Cleveland, Thomas E.; Adams, Thomas H.
CS Department Plant Pathology and Microbiology, Texas A and M University, College Station, TX, 77843, USA
SO Mol. Approaches Food Saf.: Issues Involv. Toxic Microorg., [UJNR Int. Symp.], 8th (1995), Meeting Date 1994, 263-277. Editor(s): Eklund, Mel; Richard, John L.; Mise, Katsutoshi. Publisher: Alaken, Fort Collins, Colo.
CODEN: 63EFAU
DT Conference; General Review

LA English
AB A **review** with 60 refs. Aspergillus nidulans has functioned as a model system for the study of fungal genetics since the 1950s. Application of methodologies ranging from Mendelian genetics to the most sophisticated mol. biol. techniques have resulted in detailed understanding of **genes** and pathways involved in primary metab., **secondary metab**. and development in A. nidulans. The authors have taken advantage of these traits in developing A. nidulans as a genetic system to study the mol. mechanisms regulating aflatoxin biosynthesis. Aflatoxin, a carcinogenic polyketide, is the product of a lengthy biochem. pathway found in the asexual spp., A. flavus and A. parasiticus. Aspergillus nidulans possesses most if not all of this pathway and produces sterigmatocystin, the penultimate precursor of the aflatoxin pathway. The authors have identified a .apprx.60 Kb cluster of **genes** in A. nidulans whose products are involved in sterigmatocystin biosynthesis. This cluster contains at least 20 **genes** proposed to encode both enzymic activities and regulatory proteins. The authors' results have shown that at least some of these **genes** are functionally conserved between A. nidulans, A. flavus and A. parasiticus, and that they are regulated in similar ways. Further studies of sterigmatocystin regulation in A. nidulans should yield information transferable to studies of (i) **secondary metab**. in other filamentous fungi and (ii) aflatoxin regulation in A. flavus and A. parasiticus in particular.

L5 ANSWER 8 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1996:490575 CAPLUS
DN 125:133801
TI Genomic organization and regulation of aflatoxin biosynthesis in Aspergillus flavus and A. parasiticus
AU Payne, G. A.; Bhatnagar, D.; Cleveland, T. E.; Linz, J. E.
CS North Carolina State University, Raleigh, NC, USA
SO Mol. Approaches Food Saf.: Issues Involv. Toxic Microorg., [UJNR Int. Symp.], 8th (1995), Meeting Date 1994, 249-261. Editor(s): Eklund, Mel; Richard, John L.; Mise, Katsutoshi. Publisher: Alaken, Fort Collins, Colo.
CODEN: 63EFAU
DT Conference; General Review
LA English
AB A **review** with 62 refs. Aflatoxins are toxic and carcinogenic secondary metabolites produced by Aspergillus flavus and A. parasiticus. Aflatoxin biosynthesis is complex and involves >16 enzymic steps. The pathway **genes** are clustered, and most if not all, reside within 60 kb of DNA. The function of 3 pathway **genes** (nor1, ver1, and omt1) has been clearly established. Transcription of these **genes** is regulated by aflR. This **gene**, which codes for a zinc cluster DNA binding protein, has been cloned from each fungus. Anal. of overlapping cosmid and lambda clones indicate that the genomic organization is similar for each fungus. The 4 cloned **genes** are in the order nor1, aflR, ver1, omt1. Several other regions within this cluster code for transcripts that accumulate during aflatoxin biosynthesis. Two transcripts are encoded by **genes** residing between aflR and ver1, and two are encoded by **genes** downstream of omt1. The enzyme activities involved in polyketide backbone synthesis have not been fully characterized, however, three regions within the cluster have been identified that encode for large transcripts (6.5-7.5 Kb). Two of these coding regions (ORF 7.5 and ORF 6.5) reside between nor1 and aflR and the other (ORF 7.0) is approx. 1 Kb upstream of nor1. The peptide sequence of ORF 7.5 shows strong similarity to that of yeast FAS1, and the nucleotide sequence of ORF 7.0 shows strong similarity to

that of the A. nidulans wA **gene**. Disruption of either of these **genes** prevents aflatoxin accumulation. This pathway is becoming the best characterized pathway of **secondary metab**. in filamentous fungi.

L5 ANSWER 9 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1996:329508 CAPLUS
DN 125:5103
TI Microbial **secondary metabolism**: The new frontier
AU Demain, Arnold L.
CS Department Biology, Massachusetts Institute Technology, Cambridge, MA, 02139, USA
SO Sekundaermetab. Mikroorg., [Proc. Int. Conf. Microb. Second. Metab.] (1995), Meeting Date 1994, 9-35. Editor(s): Kuhn, Willi; Fiedler, Hans-Peter. Publisher: Attempto Verlag, Tuebingen, Germany. CODEN: 62XFAG
DT Conference; General Review
LA English
AB A **review** with many refs. Microbial secondary metabolites are the low mol. mass products of **secondary metab**. They include antibiotics, pigments, toxins, effectors of ecol. competition and symbiosis, pheromones, enzyme inhibitors, immunomodulating agents, receptor antagonists and agonists, pesticides, antitumor agents and growth promotants of animals and plants. They have a major effect on the health, nutrition and economics of our society. They have unusual structures and their formation is regulated by nutrients, growth rate, feedback control, enzyme inactivation, and induction. Regulation is influenced by unique low mol. mass compds., tRNA, sigma factors and **gene** products formed during post-exponential development. The synthases of **secondary metab**. are often coded by clustered **genes** on chromosomal DNA and infrequently on plasmid DNA. Unlike primary metab., the pathways of **secondary metab**. are still not understood to a great degree and thus provide a new frontier for basic investigations of enzymol., control and differentiation.

L5 ANSWER 10 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1994:477884 CAPLUS
DN 121:77884
TI A-factor as a microbial hormone that controls cellular differentiation and **secondary metabolism** in Streptomyces griseus
AU Horinouchi, Sueharu; Beppu, Teruhiko
CS Department of Agricultural Chemistry, University of Tokyo, Tokyo, 113, Japan
SO Mol. Microbiol. (1994), 12(6), 859-64 CODEN: MOMIEE; ISSN: 0950-382X
DT Journal; General Review
LA English
AB A **review** with 34 refs. A-factor, contg. a .gamma.-butyrolactone in its structure, is an autoregulatory factor or a microbial hormone controlling **secondary metab**. and cellular differentiation in Streptomyces griseus. A-factor exerts its regulatory role by binding to a specific receptor protein which, in the absence of A-factor, acts as a repressor-type regulator for morphol. and physiol. differentiation. In the signal relay leading to a streptomycin prodn. in S. griseus, the A-factor signal is transferred from the A-factor receptor to the upstream activation sequence of a regulatory **gene**, strR,

in the streptomycin biosynthetic **gene** cluster via an A-factor-dependent protein that serves as a transcription factor for strR. The StrR protein thus induced appears to activate the transcription of other streptomycin-prodn. **genes**. The presence of A-factor homologues in a wide variety of Streptomyces species and distantly related bacteria implies the generality of .gamma.-butyrolactones as chem. cellular signaling mols. in microorganisms.

=> d 11-20 bib ab

L5 ANSWER 11 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1995:27948 CAPLUS
DN 122:74678
TI The genetics of chemical diversity
AU Cerda-Olmedo, Enrique
CS Dep. Genet., Univ. Sevilla, Seville, Spain
SO Crit. Rev. Microbiol. (1994), 20(2), 151-60
CODEN: CRVMAC; ISSN: 1040-841X
DT Journal; General Review
LA English
AB The plethora of natural org. chems. contrasts with the relative scarcity of **genes** and the apparent difficulty to evolve new ones. The genetical anal. of metab. may be reviewed with this paradox in mind. The terpenoids constitute a particularly varied group of natural compds.; many of them are dispensable to the cell and their biosynthesis is amenable to mutational anal. and other genetical and chem. methods. The prodn. of carotene and gibberellins by the fungi Phycomyces blakesleeanus and Gibberella fujikuroi, resp., seems to require an unexpectedly small no. of **genes**. A no. of **gene**-saving devices are detected that may have general validity for other cases of **secondary metab**. The most important one is versatile **genes** whose products are specific for a chem. reaction but not for the substrate. This versatility allows a combinatorial use that increases chem. and behavioral diversity. Phys. sepn. of cellular functions in compartments or enzyme aggregates not only makes processes more efficient but helps avoid some deleterious consequences of enzyme versatility.

L5 ANSWER 12 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1995:15788 CAPLUS
DN 122:97271
TI Molecular mechanism of **gene** expression for **secondary metabolism** in higher plants
AU Saito, Kazuki
CS Fac. Pharm. Sci., Chiba Univ., Chiba, 263, Japan
SO Yakugaku Kenkyu no Shinpo (1994), 10, 113-24
CODEN: YAKSEY; ISSN: 0914-4544
DT Journal; General Review
LA Japanese
AB A **review** with 23 refs. of the author's studies on the **gene** expression for plant primary and **secondary metab**. including the biosynthesis of cysteine/nonprotein amino acids and qunalizidine alkaloids.

L5 ANSWER 13 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1994:697101 CAPLUS

DN 121:297101
TI Genetic modification of plant **secondary metabolism**: alteration of product levels by overexpression of amino acid decarboxylases
AU Berlin, J.; Fecker, L.; Herminghaus, S.; Ruegenhagen, C.
CS GBF -- Gesellschaft fuer Biotechnologische Forschung m.b.H., Braunschweig, D-38124, Germany
SO Stud. Plant Sci. (1994), 4(Advances in Plant Biotechnology), 57-81 CODEN: SPLCEU; ISSN: 0928-3420
DT Journal; General Review
LA English
AB A **review** with 94 refs. Levels of target compds. of plant secondary pathways can be increased by genetic modification of enzyme activities provided sufficient information has been gathered justifying such an operation. In the first system, the product levels of serotonin were increased up to 10-fold in transgenic suspension and root cultures of Peganum harmala expressing a cDNA encoding tryptophan decarboxylase of Catharanthus roseus. In the second system, overexpression of a bacterial lysine decarboxylase **gene** led to manifold increases of the minor alkaloid anabasine in hairy root cultures and plantlets of several Nicotiana species. Common to both systems is that the decarboxylase activities are rate-limiting in the biosynthesis of serotonin and anabasine, resp.

L5 ANSWER 14 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1992:404194 CAPLUS
DN 117:4194
TI Regulation of **genes** in **secondary metabolism**
AU Yamada, Yasuyuki; Hashimoto, Takashi
CS Fac. Agric., Kyoto Univ., Kyoto, 606-01, Japan
SO Tanpakushitsu Kakusan Koso (1992), 37(7), 1326-33 CODEN: TAKKAJ; ISSN: 0039-9450
DT Journal; General Review
LA Japanese
AB A **review** with 55 refs. on expression regulation of enzyme **genes**, esp. in formation of flavonoids by higher plants.

L5 ANSWER 15 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1993:18903 CAPLUS
DN 118:18903
TI Carbon-carbon bond formation in **secondary metabolism** of microorganism. From sugars to cyclitols
AU Kakinuma, Katsumi; Yamauchi, Noriaki
CS Fac. Sci., Tokyo Inst. Technol., Tokyo, 152, Japan
SO Farumashia (1992), 28(10), 1124-9 CODEN: FARUAW; ISSN: 0014-8601
DT Journal; General Review
LA Japanese
AB A **review** with 24 refs. on the C-C bond formation of cyclitol-related secondary metabolites from a view ofenzyme and **gene** levels. Historical background of carbocyclic formation of cyclitol moiety in aminoglycosides, construction of cell-free system for the synthesis of 2-deoxy-scyllo-inosose, transformation from sugars to carbocyclic compds. having multiple functions in **secondary metab.**, and intracellular C-C bond formation of A factor (streptomycin formation regulator) and related compds. are described.

L5 ANSWER 16 OF 46 MEDLINE

AN 93073717 MEDLINE
DN 93073717
TI Autoregulatory factors and communication in actinomycetes.
AU Horinouchi S; Beppu T
CS Department of Agricultural Chemistry, University of Tokyo, Japan..
SO ANNUAL REVIEW OF MICROBIOLOGY, (1992) 46 377-98. Ref: 57
Journal code: 6DV. ISSN: 0066-4227.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
.(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199302
AB The ability to produce a wide variety of secondary metabolites and a mycelial form of growth that develops into spores are two biological aspects characteristic of the gram-positive bacterial genus Streptomyces. **Secondary metabolism** and cell differentiation are controlled by diffusible low-molecular-weight chemical substances called autoregulators. A-factor, the representative of the autoregulators, triggers streptomycin production and aerial-mycelium formation in Streptomyces griseus. A-factor exerts its regulatory function with the aid of a receptor protein that itself acts as a repressor-type regulator. The A-factor signal via the A-factor-receptor protein is transferred to downstream **genes**, such as streptomycin-production **genes** and sporulation **genes**, through multiple regulatory **genes** in a complex regulatory cascade. Thus, A-factor can be termed a "microbial hormone." This **review** deals with the A-factor-regulatory cascade as a model system for other autoregulators. The biosynthesis of A-factor, the structures and characteristics of other autoregulators, and the importance of these autoregulators in the ecosystem are also included.

L5 ANSWER 17 OF 46 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1992:191984 BIOSIS
DN BA93:102934
TI TRANSGENIC MEDICINAL PLANTS AGROBACTERIUM-MEDIATED FOREIGN **GENE** TRANSFER AND PRODUCTION OF SECONDARY METABOLITES.
AU SAITO K; YAMAZAKI M; MURAKOSHI I
CS FAC. PHARMACEUTICAL SCI., CHIBA UNIV., CHIBA 260, JAPAN.
SO J NAT PROD (LLOYDIA), (1992) 55 (2), 149-162.
CODEN: JNPRDF. ISSN: 0163-3864.
FS BA; OLD
LA English
AB Agrobacterium-Ti/Ri plasmids are natural **gene** vectors, by which a number of attempts have been made in genetic engineering of **secondary metabolism** in pharmaceutically important plants in the last few years. Opines are biosynthesized by transformed crown galls and hair roots integrated with T-DNAs of Ti/Ri plasmids. These opines are classified into five families according to their structures and biogenesis. The production of opines is a natural example of genetic engineering of the biosynthetic machinery of plant cells for the benefit of the bacterial pathogen. One recent advance in transgenic technology of potential value to pharmacology is an application of transgenic organ cultures such as hairy roots and shooty teratomas to over-production and biotransformation of secondary metabolites. The hairy roots induced by Ri plasmid of Agrobacterium rhizogenes have been proved to be an efficient

means of producing secondary metabolites that are normally biosynthesized in roots of differentiated plants. So far the specific metabolites produced by hairy root cultures and/or plants regenerated from hairy roots of 63 species have been analyzed and reported. As an alternative means of producing metabolites normally produced in leaves of plants, the shoot teratomas incited by the tumor-forming Ti plasmid or a shooty mutant of Agrobacterium tumefaciens have been used for the de novo biosynthesis and biotransformation of some specific secondary products. A second and more direct way to manipulate secondary pathways is performed by transferring and expressing specifically modified **genes** into medicinal plant cells with Agrobacterium vector systems. The **genes** encoding neomycin phosphotransferase and .beta.-glucuronidase have been used as model **genes** under the transcriptional control of appropriate promoters. Recently some specific **genes** that can eventually modify the fluxes of **secondary metabolism** have been integrated and expressed in medicinal plant cells. Future prospects are also discussed.

L5 ANSWER 18 OF 46 CAPLUS COPYRIGHT 1999 ACS
AN 1993:555545 CAPLUS
DN 119:155545
TI Genetic regulation of secondary metabolic pathways in Streptomyces
AU Chater, Keith F.
CS John Innes Cent., John Innes Inst., Norwich, NR4 7UH, UK
SO Ciba Found. Symp. (1992), 171(Secondary Metabolites: Their Function and Evolution), 144-62
CODEN: CIBSB4; ISSN: 0300-5208
DT Journal; General Review
LA English
AB A **review** with 52 refs. Streptomyces species are (along with the fungi) the best-known antibiotic-producing organisms. Often, they make several different antibiotics. The biosynthesis of each antibiotic is encoded by a complex **gene** cluster that usually also contains regulatory and resistance **genes**. Typically, there may be more than one such pathway-specific regulatory **gene** per cluster. Both activator and repressor **genes** are known. Some of the regulatory **genes** for different pathways are related. In S. coelicolor, expression of several such biosynthetic **gene** clusters also depends on at least 11 globally acting **genes**, at least one of which is involved in the translation of a rare codon (UUA). A protein phosphorylation cascade also seems to be involved. **Gene** clusters closely similar to those for the biosynthesis of arom. polyketide antibiotics det. spore pigment in some species. These **genes** show different regulation from antibiotic prodn. **genes**. The evolution of **gene** clusters for polyketide antibiotics, and the possible adaptive benefits of **secondary metab.**, are discussed.

L5 ANSWER 19 OF 46 MEDLINE DUPLICATE 1
AN 92307419 MEDLINE
DN 92307419
TI **Secondary metabolism**, inventive evolution and biochemical diversity--a **review**.
AU Vining L C
CS Biology Department, Dalhousie University, Halifax, N.S., Canada..
SO GENE, (1992 Jun 15) 115 (1-2) 135-40. Ref: 26
Journal code: FOP. ISSN: 0378-1119.
CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199210
AB Evidence now being obtained through nucleotide (nt) sequence analysis supports the concept that **secondary metabolism** has arisen by modification of existing primary metabolic reactions. Although amino acid sequence identity deduced from nt sequences of **genes** encoding proteins from related primary and secondary metabolic pathways is sufficient to indicate a common ancestry, the match is often better when **genes** in different rather than in the same species are compared. The information so far available suggests that **gene** transfer between organisms has been an important factor in the evolution of **secondary metabolism**. Many secondary pathways may be of relatively ancient origin and they may have arisen only infrequently. Much subsequent elaboration of the pathways has probably taken place after their acquisition by other species and so has been influenced by a variety of selective conditions. The characteristic diversity of secondary metabolites and their functions can be accounted for by the random manner in which the pathways initially evolved and have subsequently been exploited.

L5 ANSWER 20 OF 46 MEDLINE DUPLICATE 2
AN 92239063 MEDLINE
DN 92239063
TI Clusters of **genes** for the biosynthesis of antibiotics: regulatory **genes** and overproduction of pharmaceuticals.
AU Martin J F
CS Department of Ecology, Genetics and Microbiology, Faculty of Biology, University of Leon, Spain.
SO JOURNAL OF INDUSTRIAL MICROBIOLOGY, (1992 Feb-Mar) 9 (2) 73-90. Ref: 99
Journal code: ALF. ISSN: 0169-4146.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; B
EM 199208
AB In the last decade numerous **genes** involved in the biosynthesis of antibiotics, pigments, herbicides and other secondary metabolites have been cloned. The **genes** involved in the biosynthesis of penicillin, cephalosporin and cephamycins are organized in clusters as occurs also with the biosynthetic **genes** of other antibiotics and secondary metabolites (see **review** by Martin and Liras [65]). We have cloned **genes** involved in the biosynthesis of beta-lactam antibiotics from five different beta-lactam producing organisms both eucaryotic (Penicillium chrysogenum, Cephalosporium acremonium (syn. Acremonium chrysogenum) Aspergillus nidulans) and procaryotic (Nocardia lactamdurans, Streptomyces clavuligerus). In P. chrysogenum and A. nidulans the organization of the pcbAB, pcbC and penDE **genes** for ACV synthetase, IPN synthase and IPN acyltransferase showed a similar arrangement. In A. chrysogenum two different clusters of **genes** have been cloned. The cluster of early **genes** encodes ACV synthetase and IPN synthase, whereas the cluster of late **genes**

encodes deacetoxycephalosporin C synthetase/hydroxylase and deacetylcephalosporin C acetyltransferase. In N. lactamdurans and S. clavuligerus a cluster of early cephamycin **genes** has been fully characterized. It includes the lat (for lysine-6-aminotransferase), pcbAB (for ACV synthase) and pcbC (for IPN synthase) **genes**. Pathway-specific regulatory **genes** which act in a positive (or negative) form are associated with clusters of **genes** involved in antibiotic biosynthesis. In addition, widely acting positive regulatory elements exert a pleiotropic control on **secondary metabolism** and differentiation of antibiotic producing microorganisms. The application of recombinant DNA techniques will contribute significantly to the improvement of fermentation organisms.

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  *    July 06,1999  for U.S. Patent Image Data.                      *
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            14 COMBINATORIALS
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                 (COMBINATORIAL OR COMBINATORIALS)
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         12643 CDNA
          4370 CDNAS
         12801 CDNA
                 (CDNA OR CDNAS)
L2        1318 L1 (P) (GENOM? OR CDNA)

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US PAT NO:      5,919,900 [IMAGE AVAILABLE]              L2: 1 of 1318

DETDESC:

DETD(326)

 Genomic DNA or cDNA libraries are formed using standard
procedure (for example see Molecular Cloning. A Laboratory Manual.
Sambrook, J., Fritsch, EF., and Maniatis, T. 2nd Ed. Cold Spring Harbor
Laboratory Press, Cold Springs Harbor, N.Y. 1989). These libraries
may be from any animal, fungal, bacterial or viral source, such as
Ancylostoma caninum, other Ancylostoma species, other helminths and
mammals including human placental tissue.

DETDESC:

DETD(327)

 Such libraries are screened for useful clones by nucleic acid
hybridization using NIF cDNA sequences isolated from Ancylostoma as
probe. For example, NIF cDNA fragments of about 100-2000 base pairs
labeled for detection by standard procedure (for example, see Molecular
Cloning. A Laboratory Manual..  .  .  EF., and Maniatis, T. 2nd Ed. Cold
Spring Harbor Laboratory Press, Cold Springs Harbor, N.Y. 1989) is
hybridized with a library from another tissue or another species
under conditions of variable stringency. More preferably, however,
```

reduced stringency hybridization conditions are utilized (eg 6.times. SSC [SSC is 150. . .

DETDESC:

DETD(388)

A full-length A. ceylanicum NIF gene was isolated by screening a **cDNA library** using as hybridization probe a PCR fragment effected from the same **species**. The PCR fragment was obtained using primers that target sequences which are highly conserved among the seven A. caninum NIF. . .

US PAT NO: 5,919,691 [IMAGE AVAILABLE] L2: 2 of 1318

SUMMARY:

BSUM(41)

A homologue of the enzyme may be isolated by preparing a **genomic** or **cDNA library** of a cell of the **species** in question, and screening for DNA sequences coding for all or part of the homologue by using synthetic oligonucleotide probes. . .

US PAT NO: 5,919,681 [IMAGE AVAILABLE] L2: 3 of 1318

SUMMARY:

BSUM(8)

Recently, . . . been used to produce catalytic antibodies (see Smiley et al., "Selection of catalytic antibodies for a biosynthetic reaction from a **combinatorial cDNA library** by complementation of an auxotrophic Escherichia coli:antibodies for orotate decarboxylation," 91(18) Proceedings of the National Academy of Sciences of the. . . States of America 8319-23(1994), which is incorporated herein by reference; Janda et al., "Direct selection for a catalytic mechanism from **combinatorial** antibody **libraries**," 91(7) Proceedings of the National Academy of Sciences of the United States of America 2532-6), which is incorporated herein by. . .

US PAT NO: 5,919,656 [IMAGE AVAILABLE] L2: 4 of 1318

DETDESC:

DETD(21)

Where . . . only a portion of the 5' flanking sequence is known, it may be obtained using PCR and/or by screening a **genomic library** with suitable oligonucleotide and/or 5' flanking sequence fragments from the same or another **species**.

US PAT NO: 5,916,798 [IMAGE AVAILABLE] L2: 5 of 1318

SUMMARY:

BSUM(42)

A homologue of the enzyme may be isolated by preparing a **genomic** or **cDNA library** of a cell of the **species** in question, and

screening for DNA sequences coding for all or part of the homologue by using synthetic oligonucleotide probes. . .

=> d his

```
     (FILE 'USPAT' ENTERED AT 18:40:42 ON 12 JUL 1999)
L1          2371 S LIBRARY (P) (COMBINATORIAL OR SPECIES)
L2          1318 S L1 (P) (GENOM? OR CDNA)

=> s l2 (plurality or multiple) (3a) species

MISSING OPERATOR 'L2 (PLURALITY'

=> s l2 (p) (plurality or multiple) (3a) species

       1088417 PLURALITY
          9439 PLURALITIES
       1088735 PLURALITY
                 (PLURALITY OR PLURALITIES)
        403961 MULTIPLE
         20107 MULTIPLES
        412187 MULTIPLE
                 (MULTIPLE OR MULTIPLES)
        115733 SPECIES
L3          14 L2 (P) (PLURALITY OR MULTIPLE) (3A) SPECIES

=> d 1-14 bib ab kwic
```

US PAT NO: 5,830,644 [IMAGE AVAILABLE] L3: 1 of 14
DATE ISSUED: Nov. 3, 1998
TITLE: Method for screening for agents which increase telomerase activity in a cell
INVENTOR: Michael D. West, San Carlos, CA
Jerry Shay, Dallas, TX
Woodring E. Wright, Arlington, TX
ASSIGNEE: Geron Corporation, Menlo Park, CA (U.S. corp.)
Board of Regents, The University of Texas System, Austin, TX (U.S. corp.)
APPL-NO: 08/151,477
DATE FILED: Nov. 12, 1993
ART-UNIT: 187
PRIM-EXMR: Carla J. Myers
LEGAL-REP: Kevin Kaster, Richard J. Warburg, Amy S. Hellenkamp

US PAT NO: 5,830,644 [IMAGE AVAILABLE] L3: 1 of 14

ABSTRACT:
Method and compositions are provided for the determination of telomere length and telomerase activity, as well as the ability to increase or decrease telomerase activity in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or telomerase activity. In addition, compositions are provided for intracellular inhibition of telomerase activity and means are shown for slowing or reversing the loss of telomeric repeats in aging cells.

DRAWING DESC:

DRWD(31)

FIG. 30 shows sequences of telomeric repeats from several budding yeast **species**. Specifically, telomere-enriched **libraries** were constructed from **genomic** DNA by standard methods. Uncut yeast **genomic** DNA was ligated to a blunt-ended linearized plasmid vector and then this ligated mix was digested with a restriction enzyme. . . within the vector's polylinker and within a few kilobases of at least some of the putative telomeric ends of the **species** in question. No enzymatic pre-treatment was done to produce blunt-ends of the telomeres in the **genomic** DNA prior to the initial ligations. Plasmids were then recircularized with T4DNA ligase, and transformed into E. coli cells prior to screening for putative telomere clones by colony hybridization. The **libraries** from C. maltosa, C. pseudotropicalis, two strains of C. tropicalis, and K. lactis ATCC 32143, **species** which showed **multiple** bands that cross hybridized to the C. albicans telomeric repeat probe, were screened with this probe. A cloned S. cerevisiae telomere probe (repeat unit TG.sub.2-3 (GT).sub.1-3,) was used to screen the telomere--enriched **library** from C. glabrata, whose **genomic** DNA cross--hybridized with this, but not with the C. albicans telomeric repeat probe. C. quillermondii DNA did not appreciably cross-hybridize with either the C. albicans or the S. cerevisiae telomeric probes at the stringencies tested. The telomere-enriched **library** from this **species** was screened using total **genomic** C. guillermondii DNA as a probe. This procedure can be used to identify all clones containing repetitive sequences and we reasoned that telomeres should be a reasonable percentage of the repetitive sequences found in telomere enriched **libraries**. Typically, a few hundred E. coli transformants were obtained for each small **library** and up to nine putative telomere clones were obtained from each. Nine repetitive DNA clones were obtained from C. guillermondii,. . .

US PAT NO: 5,827,657 [IMAGE AVAILABLE] L3: 2 of 14
DATE ISSUED: Oct. 27, 1998
TITLE: Direct cloning of PCR amplified nucleic acids
INVENTOR: Corinna Herrnstadt, San Diego, CA
Joseph M. Fernandez, Carlsbad, CA
Lloyd Smith, Madison, WI
David A. Mead, Madison, WI
ASSIGNEE: Invitrogen Corporation, San Diego, CA (U.S. corp.)
Molecular Biology Resources, Inc., Milwaukee, WI (U.S. corp.)
APPL-NO: 08/683,237
DATE FILED: Jul. 18, 1996
ART-UNIT: 164
PRIM-EXMR: Scott W. Houtteman
LEGAL-REP: Scully, Scott, Murphy & Presser

US PAT NO: 5,827,657 [IMAGE AVAILABLE] L3: 2 of 14

ABSTRACT:
Methods are described for producing recombinant DNA molecules from suitable host vectors and nucleic acids subjected to 3'-terminal transferase activity. In one embodiment, the method takes advantage of the single 3'-deoxy-adenosine monophosphate (dAMP) residues attached to the 3' termini of PCR generated nucleic acids. Vectors are prepared with recognition sequences that afford single 3'-terminal deoxy-thymidine

monophosphate (dTMP) residues upon reaction with a suitable restriction enzyme. Thus, PCR generated copies of genes can be directly cloned into the vectors without need for preparing primers having suitable restriction sites therein. The invention also contemplates associated plasmid vectors and kits for implementing the methods.

SUMMARY:

BSUM(7)

While . . . a clone of PCR amplified products for further analysis, modification, or synthesis of probes. For example, a number of mRNA **species** exhibit polymorphic transcripts. Alternative splicing of the mRNA **species** to give **multiple** transcripts can be unambiguously sequenced after molecular cloning of the PCR amplification products (Frohman et al., Proc. Natl. Acad. Sci. USA 85: 8998-9002 (1988)). Cloning of PCR generated samples to construct **cDNA libraries** may also be desired. Generally, a protocol entailing cloning of PCR products can be expected tG generate a smaller set. . .

US PAT NO: 5,824,485 [IMAGE AVAILABLE] L3: 3 of 14
DATE ISSUED: Oct. 20, 1998
TITLE: Methods for generating and screening novel metabolic pathways
INVENTOR: Katie A. Thompson, Del Mar, CA
Lyndon M. Foster, Carlsbad, CA
Todd C. Peterson, Chula Vista, CA
Nicole Marie Nasby, San Diego, CA
Paul Brian, San Diego, CA
ASSIGNEE: Chromaxome Corporation, San Diego, CA (U.S. corp.)
APPL-NO: 08/639,255
DATE FILED: Apr. 24, 1996
ART-UNIT: 185
PRIM-EXMR: James Ketter
ASST-EXMR: John S. Brusca

US PAT NO: 5,824,485 [IMAGE AVAILABLE] L3: 3 of 14

ABSTRACT:
The present invention relates to a novel drug discovery system for generating and screening molecular diversity. The system provides methods for mixing and cloning genetic materials from a **plurality** of **species** of organisms in **combinatorial** gene expression **libraries** to generate novel metabolic pathways and classes of compounds. The system also involves methods for pre-screening or identifying for host organisms containing a **library** that are capable of generating such novel pathways and compounds. The host organisms may be useful in drug screening for particular diseases, and in commercial production of compounds of interest. The methods of the invention are also useful in preserving the **genomes** of organisms that are known or prospective sources of drugs.

ABSTRACT:
The . . . discovery system for generating and screening molecular diversity. The system provides methods for mixing and cloning genetic materials from a **plurality** of **species** of organisms in **combinatorial** gene expression **libraries** to generate novel metabolic pathways and classes of compounds. The system also involves methods for pre-screening or identifying for host organisms containing a

library that are capable of generating such novel pathways and compounds. The host organisms may be useful in drug screening for. . . diseases, and in commercial production of compounds of interest. The methods of the invention are also useful in preserving the **genomes** of organisms that are known or prospective sources of drugs.

DETDESC:

DETD(118)

The **combinatorial** chimeric pathway expression **libraries** of the invention may be assembled according to the principles described in section 5.1.3. In order to allow the random concatenation of DNA fragments from **multiple species** of donor organisms, the procedure for **library** assembly may be modified by including the following steps: generation of smaller **genomic** DNA fragments, ligation with regulatory sequences such as promoters and terminators to form gene cassettes, and concatenation of the gene. . .

CLAIMS:

CLMS(1)

What is claimed is:

1. A **combinatorial** gene expression **library**, comprising a pool of expression constructs, each expression construct containing one or more **cDNA** or **genomic** DNA fragments, wherein the **cDNA** or **genomic** DNA fragments in the pool of expression constructs are derived from a **plurality** of **species** of donor organisms, and wherein the **cDNA** or **genomic** DNA fragments in each expression construct are operably-associated each with one or more regulatory regions that drives expression of genes encoded by the **cDNA** or **genomic** DNA fragments in an appropriate host organism.

CLAIMS:

CLMS(3)

3. A biased **combinatorial** gene expression **library**, comprising a pool of expression constructs, each expression construct containing **cDNA** or **genomic** DNA fragments preselected from a **plurality** of **species** of donor organisms for a specific property, in which the **cDNA** or **genomic** DNA fragments are operably-associated with one or more regulatory regions that drive expression of genes encoded by the **cDNA** or **genomic** DNA fragments in an appropriate host organism.

CLAIMS:

CLMS(19)

19. A method for making a **combinatorial** gene expression **library**, comprising ligating a DNA vector to one or more **cDNA** or **genomic** DNA fragments to generate a **library** of expression constructs, wherein the **cDNA** or **genomic** DNA fragments in the **library** of expression constructs are obtained from a **plurality** of **species** of donor organisms, and wherein genes contained in the **cDNA** or **genomic** DNA fragments are operably-associated with their native or exogenous regulatory regions which drive expression of the genes in an appropriate. . .

CLAIMS:

CLMS(21)

21. A method for making a biased **combinatorial** gene expression **library**, comprising ligating a DNA vector to one or more **cDNA** or **genomic** DNA fragments to generate a **library** of expression constructs, wherein the **cDNA** or **genomic** DNA fragments are obtained from a **plurality** of **species** of donor organisms and are selected for a specific property, and wherein genes contained in the **cDNA** or **genomic** DNA fragments are operably-associated with their native or exogenous regulatory regions which drive expression of the genes in an appropriate. . .

US PAT NO: 5,817,461 [IMAGE AVAILABLE] L3: 4 of 14
DATE ISSUED: Oct. 6, 1998
TITLE: Methods and compositions for diagnosis of hyperhomocysteinemia
INVENTOR: Richard C. Austin, Ancaster, Canada
Jack Hirsh, Hamilton, Canada
Jeffrey I. Weitz, Hamilton, Canada
ASSIGNEE: Hamilton Civic Hospitals Research Development Inc., Hamilton, Canada (foreign corp.)
APPL-NO: 08/582,261
DATE FILED: Jan. 3, 1996
ART-UNIT: 187
PRIM-EXMR: W. Gary Jones
ASST-EXMR: Debra Shoemaker
LEGAL-REP: Townsend and Townsend and Crew LLP

US PAT NO: 5,817,461 [IMAGE AVAILABLE] L3: 4 of 14

ABSTRACT:
A method for diagnosing hyperhomocysteinemia by molecular genetic means is disclosed.

SUMMARY:

BSUM(50)

In . . . a predetermined homocysteine-regulated mRNA, wherein the polynucleotide is affixed to a solid substrate, typically wherein the solid substrate has a **plurality** of polynucleotide **species** affixed thereto, in a spatially defined array whereby each cell typically contains a single polynucleotide **species**, with the array often comprising in excess of 1000 distinct polynucleotide **species**. The probe polynucleotide is typically affixed by covalent linkage to the solid substrate. The solid substrate constitutes an array of. . . homocysteine-regulated mRNA. Generally, the solid substrate will be less than 10 cm.sup.3 and comprise at least 1024 positionally distinct polynucleotide **species**, at least one of which is a probe polynucleotide which binds to a predetermined homocysteine-regulated mRNA. Such polynucleotides arrays on. . . diagnosis, therapeutic efficacy monitoring, forensic identification, or for sequencing (e.g., of a pool containing unknown polynucleotides; for sequencing a mammalian **genome** or **cDNA library**), or other like uses.

US PAT NO: 5,783,431 [IMAGE AVAILABLE] L3: 5 of 14
DATE ISSUED: Jul. 21, 1998
TITLE: Methods for generating and screening novel metabolic pathways
INVENTOR: Todd C. Peterson, Chula Vista, CA
Lyndon M. Foster, Carlsbad, CA
Paul Brian, San Diego, CA
ASSIGNEE: Chromaxome Corporation, San Diego, CA (U.S. corp.)
APPL-NO: 08/738,944
DATE FILED: Oct. 24, 1996
ART-UNIT: 185
PRIM-EXMR: James Ketter
ASST-EXMR: John S. Brusca
LEGAL-REP: Pennie & Edmonds LLP

US PAT NO: 5,783,431 [IMAGE AVAILABLE] L3: 5 of 14

ABSTRACT:
The present invention relates to a novel drug discovery system for generating and screening molecular diversity. The system provides methods for mixing and cloning genetic materials from a plurality of species of organisms in combinatorial gene expression libraries to generate novel metabolic pathways and classes of compounds. The system also provides mobilizable combinatorial gene expression libraries that can be transferred from one species of host organism to another for expression. Also provided are specialized cloning vectors for making mobilizable gene expression libraries. The system also involves methods for pre-screening or identifying for host organisms containing a library that are capable of generating such novel pathways and compounds.

DETDESC:

DETD(123)

The **combinatorial** chimeric pathway expression **libraries** of the invention may be assembled according to the principles described in section 5.1.3. In order to allow the random concatenation of DNA fragments from **multiple species** of donor organisms, the procedure for **library** assembly may be modified by including the following steps: generation of smaller **genomic** DNA fragments, ligation with regulatory sequences such as promoters and terminators to form gene cassettes, and concatenation of the gene. . .

CLAIMS:

CLMS(1)

What is claimed is:

1. A mobilizable **combinatorial** gene expression **library**, comprising a pool of expression constructs, each expression construct comprising a shuttle vector that replicates in different **species** or strains of host cell, said shuttle vector containing one or more **cDNA** or **genomic** DNA fragments, wherein the **cDNA** or **genomic** DNA fragments in the pool of expression constructs are derived from a **plurality** of **species** of donor organisms, and wherein the **cDNA** or **genomic** DNA fragments are each operably-associated with one or more regulatory regions that drives expression of genes encoded by the **cDNA** or **genomic** DNA fragments in an appropriate host organism.

CLAIMS:

CLMS(13)

13. A method for making a mobilizable **combinatorial** gene expression **library**, comprising ligating a shuttle vector that replicates in different **species** or strains of host cell, to one or more **cDNA** or **genomic** DNA fragments to form a pool of expression constructs, wherein said **cDNA** or **genomic** DNA fragments in the pool of expression constructs are obtained from a **plurality** of **species** of donor organisms, and wherein the genes contained in the **cDNA** or **genomic** DNA fragments are each operably-associated with their native or exogenous regulatory regions which drive expression of the genes in an. . .

CLAIMS:

CLMS(18)

18. A method for making a **combinatorial** gene expression **library** comprising transferring a pool of expression constructs in a **species** of host organism to another **species** or strain of host organism, said expression construct comprising a shuttle vector that replicates in different **species** or strains of host cell, said shuttle vector comprising one or more **cDNA** or **genomic** DNA fragments, wherein the **cDNA** or **genomic** DNA fragments in the pool of expression constructs are obtained from a **plurality** of **species** of donor organisms, and wherein the genes contained in the **cDNA** or **genomic** DNA fragments are each operably-associated with their native or exogenous regulatory regions which drive expression of the genes in an. . .

CLAIMS:

CLMS(21)

21. A method for making a biased **combinatorial** gene expression **library**, comprising ligating a DNA vector to one or more **cDNA** or **genomic** DNA fragments to generate a **library** of expression constructs, wherein the **cDNA** or **genomic** DNA fragments in the **library** are obtained from a **plurality** of **species** of donor organisms and are selected for a specific property, and wherein genes contained in the **cDNA** or **genomic** DNA fragments are each operably-associated with their native or exogenous regulatory regions which drive expression of the genes in an. . .

US PAT NO: 5,780,600 [IMAGE AVAILABLE] L3: 6 of 14
DATE ISSUED: Jul. 14, 1998
TITLE: Purified ciliary neurotrophic factor
INVENTOR: Franklin D. Collins, Boulder, CO
Leu-Fen Lin, Boulder, CO
Drzislav Mismer, Boulder, CO
Christine Ko, Boulder, CO
ASSIGNEE: Amgen Inc., Thousand Oaks, CA (U.S. corp.)
APPL-NO: 08/448,909
DATE FILED: May 24, 1995
ART-UNIT: 188
PRIM-EXMR: Marianne P. Allen
ASST-EXMR: Stephen Gucker
LEGAL-REP: Nancy A. Oleski, Ron K. Levy, Steven M. Odre

US PAT NO: 5,780,600 [IMAGE AVAILABLE] L3: 6 of 14

ABSTRACT:
A ciliary neurotrophic factor (CNTF), particularly sciatic nerve CNTF (SN-CNTF) is claimed. The SN-CNTF described herein is a single protein species and has a specific activity that increased to greater than 25,000-fold from crude extract. Amino acid data for this SN-CNTF is also provided. In addition, methods for using this data for providing SN-CNTF probes and for screening cDNA and genomic libraries are also provided. Recombinant-DNA methods for the production of SN-CNTF are described. Nucleic acid sequences encoding rabbit and human CNTF are provided. A recombinant expression system is provided for producing biologically active CNTF.

DETDESC:

DETD(14)

The . . . greater than 25,000-fold increase in specific activity from the crude extract. Further, the final product produced is a single protein **species**. This represents an increase of greater than 30-fold over the SN-CNTF, which includes **multiple** protein **species**, reported as purified in Manthrope et al, discussed above. Since SN-CNTF is partially inactivated on reverse phase HPLC, the calculation. . . the present invention, sufficient amino acid sequence has already been obtained to generate oligonucleotide probes that will facilitate screening of **cDNA** and **genomic libraries** in order to clone the animal and human genes coding for SN-CNTF.

US PAT NO: 5,773,213 [IMAGE AVAILABLE] L3: 7 of 14
DATE ISSUED: Jun. 30, 1998
TITLE: Method for conducting sequential nucleic acid hybridization steps
INVENTOR: Steven R. Gullans, Natick, MA
Ryoji Kojima, Boston, MA
Jeffrey Randall, Acton, MA
ASSIGNEE: Brigham & Women's Hospital, Boston, MA (U.S. corp.)
APPL-NO: 08/254,811
DATE FILED: Jun. 6, 1994
ART-UNIT: 187
PRIM-EXMR: Stephanie W. Zitomer
ASST-EXMR: Paul B. Tran
LEGAL-REP: Kenyon & Kenyon

US PAT NO: 5,773,213 [IMAGE AVAILABLE] L3: 7 of 14

ABSTRACT:
A method for conducting sequential nucleic acid hybridization steps is described, whereby the ability of earlier-used primers or probes to participate in subsequent hybridization steps can be minimized, even though the differences between primer lengths are relatively small. It also relates to a rapid and quantitative method for the sequential synthesis of polynucleotide sequences by using a plurality of oligonucleotide primers, with the earlier utilized primers causing a minimum of interference with the subsequent primed synthesis reactions, yet without the need for intermediate purification steps. One preferred embodiment described is a method for differential display reverse-transcription polymerase chain reaction (DDRT-PCR), wherein

complementary DNAs (cDNAs) are first synthesized using oligo-dT-primed reverse transcription (RT), and selected subsets of said cDNAs are then amplified using a second primer in a polymerase chain reaction (PCR), with a minimum degree of background being caused in the PCR step by residual amounts of the oligo-dT primer.

SUMMARY:

BSUM(28)

The . . . In addition, because the products are typically short fragments (<600 bp) that can contain repetitive sequences, they often hybridize to **multiple** mRNA **species** in a northern blot or to multiple clones in a **cDNA library**. Although significant methodological improvements have been offered [1, 2], the Liang and Pardee method still has the significant drawback that it preferentially amplifies the non-coding 3' untranslated region (3' UTR) of **cDNAs** during PCR.

US PAT NO: 5,728,561 [IMAGE AVAILABLE] L3: 8 of 14
DATE ISSUED: Mar. 17, 1998
TITLE: Genes encoding branched-chain alpha-ketoacid dehydrogenase complex from Streptomyces avermitilis
INVENTOR: Claudio D. Denoya, Groton, CT
ASSIGNEE: Pfizer Inc., New York, NY (U.S. corp.)
APPL-NO: 08/482,385
DATE FILED: Jun. 7, 1995
ART-UNIT: 185
PRIM-EXMR: James Ketter
ASST-EXMR: Irem Yucel
LEGAL-REP: Peter C. Richardson, Gregg C. Benson, Robert F. Sheyka

US PAT NO: 5,728,561 [IMAGE AVAILABLE] L3: 8 of 14

ABSTRACT:
The present invention relates to novel DNA sequences that encode for the branched-chain alpha-ketoacid dehydrogenase complex of an organism belonging to the genus Streptomyces and to novel polypeptides produced by the expression of such sequences. It also relates to novel methods of enhancing the production of natural avermectin and of producing novel avermectin through fermentation.

SUMMARY:

BSUM(15)

We . . . using a combination of two molecular genetics techniques, DNA polymerase chain reaction (PCR) and homology probing. Homology probing involves screening **cDNA** or **genomic libraries** with radioactively-labeled synthetic oligonucleotide probes corresponding to amino acid sequences of the protein. Unfortunately, this technique has certain limitations, one. . . could encode the known amino acid sequences. The template for the amplification may be any of several DNA sources, including **genomic** DNA and supercoiled forms of plasmid **libraries**. Several reports, recently published in the literature, have demonstrated the usefulness of combining the polymerase chain reaction with homology probing for the identification of a gene from **multiple species**.

US PAT NO: 5,695,932 [IMAGE AVAILABLE] L3: 9 of 14
DATE ISSUED: Dec. 9, 1997
TITLE: Telomerase activity assays for diagnosing pathogenic infections
INVENTOR: Michael D. West, Belmont, CA
Jerry Shay, Dallas, TX
Woodring Wright, Arlington, TX
Elizabeth H. Blackburn, San Francisco, CA
Michael J. McEachern, San Francisco, CA
ASSIGNEE: University of Texas System, Austin, TX (U.S. corp.)
The Regents of the University of California, Oakland, CA (U.S. corp.)
APPL-NO: 08/060,952
DATE FILED: May 13, 1993
ART-UNIT: 187
PRIM-EXMR: Eggerton A. Campbell
LEGAL-REP: Lyon & Lyon

US PAT NO: 5,695,932 [IMAGE AVAILABLE] L3: 9 of 14

ABSTRACT:
Method and compositions are provided for the determination of telomere length and telomerase activity, as well as the ability to inhibit telomerase activity in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or telomerase activity. In addition, compositions are provided for intracellular inhibition of telomerase activity and means are shown for slowing the loss of telomeric repeats in aging cells.

DRAWING DESC:

DRWD(31)

FIG. 30 shows sequences of telomeric repeats from several budding yeast **species**. Specifically, telomere-enriched **libraries** were constructed from **genomic** DNA by standard methods. Uncut yeast **genomic** DNA was ligated to a blunt-ended linearized plasmid vector and then this ligated mix was digested with a restriction enzyme. . . within the vector's polylinker and within a few kilobases of at least some of the putative telomeric ends of the **species** in question. No enzymatic pre-treatment was done to produce blunt-ends of the telomeres in the **genomic** DNA prior to the initial ligations. Plasmids were then recircularized with T4DNA ligase, and transformed into E. coli cells prior to screening for putative telomere clones by colony hybridization. The **libraries** from C. maltosa, C. pseudotropicalis, two strains of C. tropicalis, and K. lactis ATCC 32143, **species** which showed **multiple** bands that cross hybridized to the C. albicans telomeric repeat probe, were screened with this probe. A cloned S. cerevisiae telomere probe (repeat unit TG.sub.2-3 (GT).sub.1-3,) was used to screen the telomere--enriched **library** from C. glabrata, whose **genomic** DNA cross--hybridized with this, but not with the C. albicans telomeric repeat probe. C. guillermondii DNA did not appreciably cross-hybridize with either the C. albicans or the S. cerevisiae telomeric probes at the stringencies tested. The telomere--enriched **library** from this **species** was screened using total **genomic** C. guillermondii DNA as a probe. This procedure can be used to identify all clones containing repetitive sequences and we reasoned that telomeres should be a

reasonable percentage of the repetitive sequences found in telomere enriched **libraries**. Typically, a few hundred E. coli transformants were obtained for each small **library** and up to nine putative telomere clones were obtained from each. Nine repetitive DNA clones were obtained from C. guillermondii,. . .

US PAT NO: 5,645,986 [IMAGE AVAILABLE] L3: 10 of 14
DATE ISSUED: Jul. 8, 1997
TITLE: Therapy and diagnosis of conditions related to telomere length and/or telomerase activity
INVENTOR: Michael D. West, San Carlos, CA
Calvin B. Harley, Palo Alto, CA
Catherine M. Strahl, San Francisco, CA
Michael J. McEachern, San Francisco, CA
Jerry Shay, Dallas, TX
Woodring E. Wright, Arlington, TX
Elizabeth H. Blackburn, San Francisco, CA
Homayoun Vaziri, Toronto, Canada
ASSIGNEE: Board of Reagents, The University of Texas System, Dallas, TX (U.S. corp.)
The Reagents of the University of California, Oakland, CA (U.S. corp.)
Geron Corporation, Menlo Park, CA (U.S. corp.)
APPL-NO: 08/153,051
DATE FILED: Nov. 12, 1993
ART-UNIT: 187
PRIM-EXMR: W. Gary Jones
ASST-EXMR: Carla Myers
LEGAL-REP: Kevin R. Kaster, Richard J. Warburg, Amy S. Hellenkamp

US PAT NO: 5,645,986 [IMAGE AVAILABLE] L3: 10 of 14

ABSTRACT:
Method and compositions are provided for the determination of telomere length and telomerase activity, as well as the ability to increase or decrease telomerase activity in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or telomerase activity. In addition, compositions are provided for intracellular inhibition of telomerase activity and means are shown for slowing or reversing the loss of telomeric repeats in aging cells.

DRAWING DESC:

DRWD(31)

FIG. 30 shows sequences of telomeric repeats from several budding yeast **species**. Specifically, telomere-enriched **libraries** were constructed from **genomic** DNA by standard methods. Uncut yeast **genomic** DNA was ligated to a blunt-ended linearized plasmid vector and then this ligated mix was digested with a restriction enzyme. . . within the vector's polylinker and within a few kilobases of at least some of the putative telomeric ends of the **species** in question. No enzymatic pre-treatment was done to produce blunt-ends of the telomeres in the **genomic** DNA prior to the initial ligations. Plasmids were then recircularized with T4DNA ligase, and transformed into E. coli cells prior to screening for putative telomere clones by colony hybridization. The **libraries** from C. maltosa, C. pseudotropicalis, two strains of C.

tropicalis, and K. lactis ATCC 32143, **species** which showed **multiple** bands that cross hybridized to the C. albicans telomeric repeat probe, were screened with this probe. A cloned S. cerevisiae telomere probe (repeat unit TG.sub.2-3 (GT).sub.1-3',) was used to screen the telomere-enriched **library** from C. glabrata, whose **genomic** DNA cross-hybridized with this, but not with the C. albicans telomeric repeat probe. C. guillermondii DNA did not appreciably cross-hybridize with either the C. albicans or the S. cerevisiae telomeric probes at the stringencies tested. The telomere-enriched **library** from this **species** was screened using total **genomic** C. guillermondii DNA as a probe. This procedure can be used to identify all clones containing repetitive sequences and we reasoned that telomeres should be a reasonable percentage of the repetitive sequences found in telomere enriched **libraries**. Typically, a few hundred E. coli transformants were obtained for each small **library** and up to nine putative telomere clones were obtained from each. Nine repetitive DNA clones were obtained from C. guillermondii,. . .

US PAT NO: 5,487,993 [IMAGE AVAILABLE] L3: 11 of 14
DATE ISSUED: Jan. 30, 1996
TITLE: Direct cloning of PCR amplified nucleic acids
INVENTOR: Corinna Herrnstadt, San Diego, CA
Joseph M. Fernandez, Carlsbad, CA
Lloyd Smith, Madison, WI
David A. Mead, Madison, WI
ASSIGNEE: Invitrogen Corporation, San Diego, CA (U.S. corp.)
Chimer, Milwaukee, WI (U.S. corp.)
APPL-NO: 08/119,313
DATE FILED: Sep. 9, 1993
ART-UNIT: 187
PRIM-EXMR: W. Gary Jones
ASST-EXMR: Scott Houtteman
LEGAL-REP: Campbell and Flores

US PAT NO: 5,487,993 [IMAGE AVAILABLE] L3: 11 of 14

ABSTRACT:
Methods are described for producing recombinant DNA molecules from suitable host vectors and nucleic acids subjected to 3'-terminal transferase activity. In one embodiment, the method takes advantage of the single 3'-deoxy-adenosine monophosphate (dAMP) residues attached to the 3' termini of PCR generated nucleic acids. Vectors are prepared with recognition sequences that afford single 3'-terminal deoxy-thymidine monophosphate (dTMP) residues upon reaction with a suitable restriction enzyme. Thus, PCR generated copies of genes can be directly cloned into the vectors without need for preparing primers having suitable restriction sites therein. The invention also contemplates associated plasmid vectors and kits for implementing the methods.

SUMMARY:

BSUM(8)

While . . . a clone of PCR amplified products for further analysis, modification, or synthesis of probes. For example, a number of mRNA **species** exhibit polymorphic transcripts. Alternative splicing of the mRNA **species** to give **multiple** transcripts can be unambiguously sequenced after molecular cloning of the PCR amplification products (Frohman et al., Proc. Natl. Acad. Sci. USA 85: 8998-9002 (1988)).

Cloning of PCR generated samples to construct **cDNA libraries** may also be desired. Generally, a protocol entailing cloning of PCR products can be expected to generate a smaller set. . .

US PAT NO: 5,141,856 [IMAGE AVAILABLE] L3: 12 of 14
DATE ISSUED: Aug. 25, 1992
TITLE: Expression of purified ciliary neurotrophic factor
INVENTOR: Franklin D. Collins, Boulder, CO
Leu-Fen Lin, Boulder, CO
Drzislav Mismer, Boulder, CO
Christine Ko, Boulder, CO
ASSIGNEE: Synergen, Inc., Boulder, CO (U.S. corp.)
APPL-NO: 07/458,564
DATE FILED: Dec. 28, 1989
ART-UNIT: 183
PRIM-EXMR: Joan Ellis
LEGAL-REP: Beaton & Swanson

US PAT NO: 5,141,856 [IMAGE AVAILABLE] L3: 12 of 14

ABSTRACT:
A ciliary neurotrophic factor (CNTF), particularly sciatic nerve CNTF (SN-CNTF) is claimed. The SN-CNTF described herein is a single protein species and has a specific activity that increased to greater than 25,000-fold from crude extract.
Amino acid data for this SN-CNTF is also provided. In addition, methods for using this data for providing SN-CNTF probes and for screening cDNA and genomic libraries are also provided. Recombinant-DNA methods for the production of SN-CNTF are described.
Nucleic acid sequences encoding rabbit and human CNTF are provided. A recombinant expression system is provided for producing biologically active CNTF.

DETDESC:

DETD(14)

The . . . greater than 25,000-fold increase in specific activity from the crude extract. Further, the final product produced is a single protein **species**. This represents an increase of greater than 30-fold over the SN-CNTF, which includes **multiple** protein **species**, reported as purified in Manthorpe et al. discussed above. Since SN-CNTF is partially inactivated on reverse phase HPLC, the calculation. . . the present invention, sufficient amino acid sequence has already been obtained to generate oligonucleotide probes that will facilitate screening of **cDNA** and **genomic libraries** in order to clone the animal and human genes coding for SN-CNTF.

US PAT NO: 5,011,914 [IMAGE AVAILABLE] L3: 13 of 14
DATE ISSUED: Apr. 30, 1991
TITLE: Purified ciliary neurotrophic factor
INVENTOR: Franklin D. Collins, 582 Locust Pl., Boulder, CO 80302
Leu-Fen Lin, 854 Braun Ct., Golden, CO 80401
APPL-NO: 07/293,851
DATE FILED: Jan. 5, 1989
ART-UNIT: 186
PRIM-EXMR: Margaret Moskowitz
ASST-EXMR: Keith Furman

US PAT NO: 5,011,914 [IMAGE AVAILABLE] L3: 13 of 14

ABSTRACT:
A ciliary neurotrophic factor (CNTF), particularly sciatic nerve CNTF (SN-CNFT) is claimed. The SN-CNTF described herein is a single protein species and has a specific activity that increased to greater than 25,000-fold from crude extract. The purification is carried out by lowering the pH of the crude nerve extract preparation to form a precipitate which is removed and discarded; raising the pH to about 6.3 followed by ammonium sulfate fractionation; chromatofocusing a solution containing a second precipitate obtained from the 30% to 60% ammonium sulfate containing solution; subjecting the fractions obtained by chromatofocusing to sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE); and performing reversed-phase high-performance liquid chromatography (HPLC) on the SDS-PAGE eluate.
Amino acid data for this SN-CNTF is also provided. In addition, methods for using this data for providing SN-CNTF probes and for screening cDNA and genomic libraries are also provided. Recombinant-DNA methods for the production of SN-CNTF are described.

DETDESC:

DETD(10)

The . . . greater than 25,000-fold increase in specific activity from the crude extract. Further, the final product produced is a single protein **species**. This represents an increase of greater than 30-fold over the SN-CNTF, which includes **multiple** protein **species**, reported as purified in Manthorpe et al. discussed above. Since SN-CNTF is partially inactivated on reverse phase HPLC, the calculation. . . the present invention, sufficient amino acid sequence has already been obtained to generate oligonucleotide probes that will facilitate screening of **cDNA** and **genomic libraries** in order to clone the animal and human genes coding for SN-CNTF.

US PAT NO: 4,997,929 [IMAGE AVAILABLE] L3: 14 of 14
DATE ISSUED: Mar. 5, 1991
TITLE: Purified ciliary neurotrophic factor
INVENTOR: Franklin D. Collins, Boulder, CO
Leu-Fen Lin, Boulder, CO
ASSIGNEE: Synergen, Inc., Boulder, CO (U.S. corp.)
APPL-NO: 07/404,533
DATE FILED: Sep. 8, 1989
ART-UNIT: 185
PRIM-EXMR: Robin L. Teskin
LEGAL-REP: Beaton & Swanson

US PAT NO: 4,997,929 [IMAGE AVAILABLE] L3: 14 of 14

ABSTRACT:
A ciliary neurotrophic factor (CNTF), particularly sciatic nerve CNTF(SN-CNFT) is claimed. The SN-CNTF described herein is a single protein species and has a specific activity that increased to greater than 25,000-fold from crude extract.
Amino acid data for this SN-CNTF is also provided. In addition, methods for using this data for providing SN-CNTF probes and for screening cDNA and genomic libraries are also provided. Recombinant-DNA methods for the production of SN-CNTF are described.

Nucleic acid sequences encoding rabbit and human CNTF are provided. A recombinant expression system is provided for producing biologically active CNTF.

DETDESC:

DETD(14)

The . . . greater than 25,000-fold increase in specific activity from the crude extract. Further, the final product produced is a single protein **species**. This represents an increase of greater than 30-fold over the SN-CNTF, which includes **multiple** protein **species**, reported as purified in Manthorpe et al. discussed above. Since SN-CNTF is partially inactivated on reverse phase HPLC, the calculation. . . the present invention, sufficient amino acid sequence has already been obtained to generate oligonucleotide probes that will facilitate screening of **cDNA** and **genomic libraries** in order to clone the animal and human genes coding for SN-CNTF.

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         21101 LIBRARY
          9240 LIBRARIES
         23338 LIBRARY
                 (LIBRARY OR LIBRARIES)
         28392 ORGANISM
         33238 ORGANISMS
         46981 ORGANISM
                 (ORGANISM OR ORGANISMS)
L1        1135 LIBRARY (P) ORGANISM

=> s l1 (p) (genom? or cdna)

         15336 GENOM?
         12643 CDNA
          4370 CDNAS
         12801 CDNA
                 (CDNA OR CDNAS)
L2         876 L1 (P) (GENOM? OR CDNA)

=> s l2 (plurality or multiple) (3a) organism

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=> s l2 (p) (plurality or multiple) (3a) organism

       1088417 PLURALITY
          9439 PLURALITIES
       1088735 PLURALITY
                 (PLURALITY OR PLURALITIES)
        403961 MULTIPLE
         20107 MULTIPLES
        412187 MULTIPLE
                 (MULTIPLE OR MULTIPLES)
         28392 ORGANISM
         33238 ORGANISMS
         46981 ORGANISM
                 (ORGANISM OR ORGANISMS)
L3           2 L2 (P) (PLURALITY OR MULTIPLE) (3A) ORGANISM

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US PAT NO:      5,824,485 [IMAGE AVAILABLE]              L3: 1 of 2
DATE ISSUED:    Oct. 20, 1998
TITLE:          Methods for generating and screening novel metabolic
                  pathways
INVENTOR:       Katie A. Thompson, Del Mar, CA
                Lyndon M. Foster, Carlsbad, CA
```

Todd C. Peterson, Chula Vista, CA
Nicole Marie Nasby, San Diego, CA
Paul Brian, San Diego, CA
ASSIGNEE: Chromaxome Corporation, San Diego, CA (U.S. corp.)
APPL-NO: 08/639,255
DATE FILED: Apr. 24, 1996
ART-UNIT: 185
PRIM-EXMR: James Ketter
ASST-EXMR: John S. Brusca

US PAT NO: 5,824,485 [IMAGE AVAILABLE] L3: 1 of 2

ABSTRACT:
The present invention relates to a novel drug discovery system for generating and screening molecular diversity. The system provides methods for mixing and cloning genetic materials from a **plurality** of species of **organisms** in combinatorial gene expression **libraries** to generate novel metabolic pathways and classes of compounds. The system also involves methods for pre-screening or identifying for host **organisms** containing a **library** that are capable of generating such novel pathways and compounds. The host **organisms** may be useful in drug screening for particular diseases, and in commercial production of compounds of interest. The methods of the invention are also useful in preserving the **genomes** of **organisms** that are known or prospective sources of drugs.

ABSTRACT:
The . . . discovery system for generating and screening molecular diversity. The system provides methods for mixing and cloning genetic materials from a **plurality** of species of **organisms** in combinatorial gene expression **libraries** to generate novel metabolic pathways and classes of compounds. The system also involves methods for pre-screening or identifying for host **organisms** containing a **library** that are capable of generating such novel pathways and compounds. The host **organisms** may be useful in drug screening for particular diseases, and in commercial production of compounds of interest. The methods of the invention are also useful in preserving the **genomes** of **organisms** that are known or prospective sources of drugs.

DETDESC:

DETD(88)

Either DNA or RNA may be used as starting genetic material for preparing such **libraries** which may include **cDNA libraries**, **genomic** DNA **libraries**, as well as mixed **cDNA/genomic** DNA **libraries**. DNA fragments derived from a **plurality** of donor **organisms**, e.g., **organisms** described in Section 5.1.1, are introduced into a pool of host **organisms**, such that each host **organism** in the pool contains a DNA fragment derived from one of the donor **organisms**.

DETDESC:

DETD(118)

The combinatorial chimeric pathway expression **libraries** of the invention may be assembled according to the principles described in section 5.1.3. In order to allow the random concatenation of DNA

fragments from **multiple** species of donor **organisms**, the procedure for **library** assembly may be modified by including the following steps: generation of smaller **genomic** DNA fragments, ligation with regulatory sequences such as promoters and terminators to form gene cassettes, and concatenation of the gene. . .

US PAT NO: 5,783,431 [IMAGE AVAILABLE] L3: 2 of 2
DATE ISSUED: Jul. 21, 1998
TITLE: Methods for generating and screening novel metabolic pathways
INVENTOR: Todd C. Peterson, Chula Vista, CA
Lyndon M. Foster, Carlsbad, CA
Paul Brian, San Diego, CA
ASSIGNEE: Chromaxome Corporation, San Diego, CA (U.S. corp.)
APPL-NO: 08/738,944
DATE FILED: Oct. 24, 1996
ART-UNIT: 185
PRIM-EXMR: James Ketter
ASST-EXMR: John S. Brusca
LEGAL-REP: Pennie & Edmonds LLP

US PAT NO: 5,783,431 [IMAGE AVAILABLE] L3: 2 of 2

ABSTRACT:
The present invention relates to a novel drug discovery system for generating and screening molecular diversity. The system provides methods for mixing and cloning genetic materials from a plurality of species of organisms in combinatorial gene expression libraries to generate novel metabolic pathways and classes of compounds. The system also provides mobilizable combinatorial gene expression libraries that can be transferred from one species of host organism to another for expression. Also provided are specialized cloning vectors for making mobilizable gene expression libraries. The system also involves methods for pre-screening or identifying for host organisms containing a library that are capable of generating such novel pathways and compounds.

DETDESC:

DETD(94)

Either DNA or RNA may be used as starting genetic material for preparing such **libraries** which may include **cDNA libraries**, **genomic** DNA **libraries**, as well as mixed **cDNA/genomic** DNA **libraries**. DNA fragments derived from a **plurality** of donor **organisms**, e.g., **organisms** described in Section 5.1.1, are introduced into a pool of host **organisms**, such that each host **organism** in the pool contains a DNA fragment derived from one of the donor **organisms**.

DETDESC:

DETD(123)

The combinatorial chimeric pathway expression **libraries** of the invention may be assembled according to the principles described in section 5.1.3. In order to allow the random concatenation of DNA fragments from **multiple** species of donor **organisms**, the procedure for **library** assembly may be modified by including the following steps: generation of smaller **genomic** DNA fragments, ligation with

regulatory sequences such as promoters and terminators to form gene cassettes, and concatenation of the gene. . .

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